

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 10638 WO	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/IB 00/ 01380	International filing date (day/month/year) 28/09/2000	(Earliest) Priority Date (day/month/year) 28/09/1999
Applicant APPLIED RESEARCH SYSTEMS ARS HOLDING N.V.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the title,

the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the abstract,

the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 00/01380

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-10,13-22(partly)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

B x II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-10,13-22(partly)

Present claims 1-10,13-22 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of the examples and closely related homologous compounds, i.e. wherein Ar1 is substituted phenyl, X is O and Ar2 is 2,5-thienyl or 2,5-furyl.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

PC B 00/01380

IPC 7 C07D409/12 C07D333/34 C07D333/36 C07D413/12 C07D495/04
C07D471/04 C07D409/14 C07D405/12 A61K31/496 A61K31/445
//(C07D495/04,333:00,221:00)

B. FIELDS SEARCHED

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

CHEM ABS Data, WPI Data, BEILSTEIN Data, EPO-Internal, PAJ

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 30992 A (BRISTOL-MYERS SQUIBB CO.;USA) 28 August 1997 (1997-08-28) cited in the application see general formula and provisos in application ---	1-22
A	WO 97 45403 A (PHARMACIA & UPJOHN COMPANY;USA) 4 December 1997 (1997-12-04) see whole application --- -/--	1-22

☒ Patent family members are listed in annex.

"&" document member of the same patent family

21. 11. 00

Scruton-Evans, I

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 00/01380

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KELLY J ET AL: "Synthesis of isomeric 3-piperidinyl and 3-pyrrolidinyl benzo[5,6-c]cyclohepta[1,2-b]pyridines: sulfonamido derivatives as inhibitors of Ras prenylation" BIOORG. MED. CHEM. (BMECEP, 09680896); 1998; VOL.6 (6); PP.673-686, XP000881133 Schering-Plough Research Institute; Kenilworth; 07033; NJ; USA (US) the whole document ----	1-22
A	WO 98 53814 A (MERCK & CO., INC.; USA) 3 December 1998 (1998-12-03) cited in the application the whole document ----	1-22
A	WO 99 16751 A (MERCK PATENT G.M.B.H.; GERMANY) 8 April 1999 (1999-04-08) the whole document ----	1-22
A	WO 99 21859 A (GLAXO GROUP LTD ; GLENNON KIMBERLY CAROLINE (US); PEEL MICHAEL ROBE) 6 May 1999 (1999-05-06) the whole document ----	1-22
A	WO 96 30017 A (SCHERING CORP) 3 October 1996 (1996-10-03) cited in the application the whole document -----	1-22

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 00/01380

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9730992 ✓ A	28-08-1997	AU 718676 B	20-04-2000
		AU 2136697 A	10-09-1997
		BG 102738 A	30-09-1999
		BR 9707614 A	27-07-1999
		CN 1214685 A	21-04-1999
		CZ 9802696 A	13-10-1999
		EP 0892797 A	27-01-1999
		HU 9902016 A	28-09-1999
		JP 2000502356 T	29-02-2000
		LT 98120 A,B	25-06-1999
		LV 12150 A	20-10-1998
		LV 12150 B	20-12-1998
		NO 983892 A	25-08-1998
		PL 328868 A	01-03-1999
		US 6011029 A	04-01-2000
		ZA 9701621 A	25-08-1998
WO 9745403 ✓ A	04-12-1997	AU 720414 B	01-06-2000
		AU 3060197 A	05-01-1998
		CN 1217711 A	26-05-1999
		CZ 9803701 A	12-05-1999
		EP 0923542 A	23-06-1999
		FI 982572 A	27-11-1998
		NO 985599 A	30-11-1998
		PL 330207 A	26-04-1999
WO 9853814 ✓ A	03-12-1998	EP 1001764 A	24-05-2000
WO 9916751 ✓ A	08-04-1999	DE 19743435 A	08-04-1999
		AU 9540798 A	23-04-1999
		BR 9812699 A	22-08-2000
		EP 1025086 A	09-08-2000
		NO 20001687 A	31-03-2000
		ZA 9808937 A	31-03-1999
WO 9921859 ✓ A	06-05-1999	AU 1151099 A	17-05-1999
WO 9630017 ✓ A	03-10-1996	US 5684013 A	04-11-1997
		AU 708244 B	29-07-1999
		AU 5307296 A	16-10-1996
		CA 2216291 A	03-10-1996
		EP 0814807 A	07-01-1998
		HU 9801396 A	28-05-1999
		JP 3001982 B	24-01-2000
		JP 10505102 T	19-05-1998
		US 5703090 A	30-12-1997
		US 5958939 A	28-09-1999

4

TENT COOPERATION TR

Y

REC'D 25 OCT 2001

WIPO

PCT

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14

Applicant's or agent's file reference 10638 WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/IB00/01380	International filing date (day/month/year) 28/09/2000	Priority date (day/month/year) 28/09/1999
International Patent Classification (IPC) or national classification and IPC C07D409/12		
Applicant APPLIED RESEARCH SYSTEMS ARS HOLDING N.V. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 7 sheets, including this cover sheet.

- ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 20/04/2001	Date of completion of this report 23.10.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Scruton-Evans, I Telephone No. +49 89 2399 8272



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB00/01380

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-89 as originally filed

Claims, No.:

1 (part), 2 (part), as originally filed
3-22

1 (part), as received on 06/10/2001 with letter of 04/10/2001
2 (part)

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB00/01380

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-10,13-22(partly).

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-10,13-22(partly).

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 1-22
 No: Claims

Inventive step (IS) Yes: Claims 11,12

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/IB00/01380

	No:	Claims	1-10,13-22
Industrial applicability (IA)	Yes:	Claims	1-22
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

With regard to the patentability of the present application, it is to be noted that as only an incomplete search was carried out (see search report), so this report relates only to that part of the application that has been searched. It is considered to be of importance that all of the examples provided have a 2,5thienyl or 2,5-furyl for Ar₂, and nearly all have phenyl for Ar₁.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

- 1) The following documents cited in the Search Report are referred to in this communication;

D1: WO 97 30992 A (BRISTOL-MYERS SQUIBB CO.;USA) 28 August 1997 (1997-08-28)

D2: WO 97 45403 A (PHARMACIA & UPJOHN COMPANY;USA) 4 December 1997 (1997-12-04)

D3: WO 98 53814 A (MERCK & CO., INC.;USA) 3 December 1998 (1998-12-03)

D4: WO 99 16751 A (MERCK PATENT G.M.B.H.;GERMANY) 8 April 1999 (1999-04-08)

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/IB00/01380

D5: WO 99 21859 A (GLAXO GROUP LTD ;GLENNON KIMBERLY CAROLINE (US); PEEL MICHAEL ROBE) 6 May 1999 (1999-05-06)

D6: KELLY J ET AL: 'Synthesis of isomeric 3-piperidinyl and 3-pyrrolidinyl benzo[5,6]cyclohepta[1,2-b]pyridines: sulfonamido derivatives as inhibitors of Ras prenylation' BLOORG. MED. CHEM. (BMECEP,09680896);1998; VOL.6 (6); PP.673-686, XP000881133 Schering-Plough Research Institute;Kenilworth; 07033; NJ; USA (US)

D7 WO9630017

- 2) With regard to the requirement for novelty (Article 33(2) of the PCT), the compounds disclosed in the documents D1-D4 and D6 are excluded from the compound claim of claim 1 and the first medical use claim of claim 2 (the correction of the proviso relating to D2 to cyclopent[f]isoindol from cyanopent[f]isoindole is accepted). For the second medical use claim 13, as none of the documents D1-D4 and D6 disclose such a use, this can also be considered to be novel. On page 36 of the description, the reason for the first two provisos in claim 1 is given, and it is assumed that such compounds are not active, as stated, as claim 2 does not include these provisos. Article 33(2) of the PCT thus appears to have been satisfied for that matter which has been searched.
- 4) With regard to the requirement for inventive step (Article 33(3) of the PCT), the only comments made are with respect to the actual matter searched. The problem underlying the present application is considered to have been the provision of novel compounds which modulate the JNK pathway. The solution provided by the Applicant is the examples

of the application, which have been representatively shown to indeed solve the problem. As the closest structural prior arts have no such activity, and D5 has a completely different structure, that the compounds prepared and tested should have such an activity can be considered to be non-obvious, but the Examining Division does not consider that the problem can be assessed for claim 1 in its entirety, and thus only claims 11,12 can be considered at this stage to satisfy the requirements of Article 33(3) of the PCT, as only a reasonable generalisation over the examples provided and tested can be justified.

Re Item VII

Certain defects in the international application

The terms "substituted" used in the claims would have to be defined according to the description if a generic claim was filed.

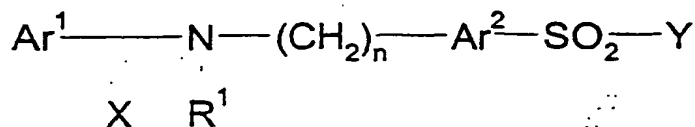
The preferred and most preferred embodiments in the claims should be made the subject of dependent claims

with the further proviso that if X is oxygen, R¹ is hydrogen and n is 1, while Y is a piperazine, said piperazine at the para-nitrogen shall not be substituted by a group containing a benzamidine or a protected form thereof;

with the further proviso that the compounds 2-{[2-(benzoylaminoethyl)-
5 thiophene]-5-sulfonyl}-1,2,3,5,6,7-hexahydro-N,N-dipropylcyclopentylisoin-
dol-6-amine and N-[[5-[[7-cyano-1,2,3,5-tetrahydro-1-(1H-imidazol-4-yl-
methyl)-3-(phenylmethyl)-4H-1,4-benzodiazepin-4-yl]sulfonyl]-2-thienyl]
methyl] benzamide and its hydrochloride are excluded;

with the final proviso that if X is oxygen and Y is a 4-8 membered saturated cy-
10 clic alkyl containing one or two nitrogen atoms, Y shall not be substituted by a
group (C=O)N(R,R') at the α-position of the sulfonamide nitrogen.

2. Sulfonamide derivatives according to formula I



with its geometrical isomers, in an optically active form as enantiomers, dia-
15 stereomers, as well as in the form of racemates, as well as pharmaceutically ac-
ceptable salts thereof, wherein

Ar¹ and Ar² are independently from each other substituted or unsubstituted aryl
or heteroaryl groups,

X is O or S, preferably O;

20 R¹ is hydrogen or a C₁-C₆-alkyl group, or R¹ forms a substituted or unsubstituted
5-6-membered saturated or unsaturated ring with Ar¹;

n is an integer from 0 to 5, preferably between 1-3 and most preferred 1;

Y within formula I is an unsubstituted or a substituted 4-12-membered saturated
cyclic or bicyclic alkyl containing at least one nitrogen atom, whereby one ni-
25 trogen atom within said ring is forming a bond with the sulfonyl group of for-
mula I thus providing a sulfonamide, for use as a medicament;

with the proviso that if Y is a piperidino- or a pyrrolidino group being substitu-
ted at the β-position of the piperidino- or a pyrrolidino nitrogen by a benzo[5,
6]cyclohepta[1, 2b]pyridine, or a benzo[5, 6]cyclohept (3,4) ene [1, 2b]pyridine,

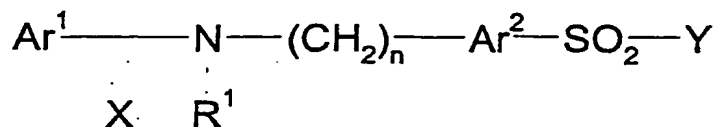
REPLACES
ART 34 AMOT

with the further proviso that if X is oxygen, R¹ is hydrogen and n is 1, while Y is a piperazine, said piperazine at the para-nitrogen shall not be substituted by a group containing a benzamidine or a protected form thereof;

with the further proviso that the compounds 2-{[2-(benzoylaminomethyl)-thiophene]-5-sulfonyl}-1,2,3,5,6,7-hexahydro-N,N-dipropylcyanopent[*f*]isoin-
dol-6-amine and N-[[5-[[7-cyano-1,2,3,5-tetrahydro-1-(1H-imidazol-4-yl)-methyl]-3-(phenylmethyl)-4H-1,4-benzodiazepin-4-yl]sulfonyl]-2-thienyl] methyl] benzamide and its hydrochloride are excluded;

with the final proviso that if X is oxygen and Y is a 4-8 membered saturated cyclic alkyl containing one or two nitrogen atoms, Y shall not be substituted by a group (C=O)N(R,R') at the α-position of the sulfonamide nitrogen.

2. Sulfonamide derivatives according to formula I



I

with its geometrical isomers, in an optically active form as enantiomers, diastereomers, as well as in the form of racemates, as well as pharmaceutically acceptable salts thereof, wherein

Ar¹ and Ar² are independently from each other substituted or unsubstituted aryl or heteroaryl groups,

X is O or S, preferably O;

R¹ is hydrogen or a C₁-C₆-alkyl group, or R¹ forms a substituted or unsubstituted 5-6-membered saturated or unsaturated ring with Ar¹;

n is an integer from 0 to 5, preferably between 1-3 and most preferred 1;

Y within formula I is an unsubstituted or a substituted 4-12-membered saturated cyclic or bicyclic alkyl containing at least one nitrogen atom, whereby one nitrogen atom within said ring is forming a bond with the sulfonyl group of formula I thus providing a sulfonamide, for use as a medicament;

with the proviso that if Y is a piperidino- or a pyrrolidino group being substituted at the β-position of the piperidino- or a pyrrolidino nitrogen by a benzo[5, 6]cyclohepta[1, 2b]pyridine, or a benzo[5, 6]cyclohept (3,4) ene [1, 2b]pyridine,



(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
5 April 2001 (05.04.2001)

PCT

(10) International Publication Number
WO 01/23378 A1

(51) International Patent Classification⁷: C07D 409/12,
333/34, 333/36, 413/12, 495/04, 471/04, 409/14, 405/12,
A61K 31/496, 31/445 // (C07D 495/04, 333:00, 221:00)

Plan-les-Orates (CH). GOTTELAND, Jean-Pierre
[FR/FR]; 423, chemin des Crets, F-74160 Beaumont
(FR). BIAMONTE, Marco [US/CH]; 13, rue St. Joseph,
CH-1227 Carouge (CH).

(21) International Application Number: PCT/IB00/01380

(74) Agents: MOINAS, Michel et al.; Moinas Savoye &
Cronin, 42, rue Plantamour, CH-1201 Geneva (CH).

(22) International Filing Date:
28 September 2000 (28.09.2000)

(25) Filing Language: English

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,
DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(26) Publication Language: English

(30) Priority Data:
99810869.0 28 September 1999 (28.09.1999) EP

(71) Applicant (*for all designated States except US*): AP-
PLIED RESEARCH SYSTEMS ARS HOLDING N.V.
[NL/NL]; Pietermaai 15, Curacao (AN).

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(72) Inventors; and

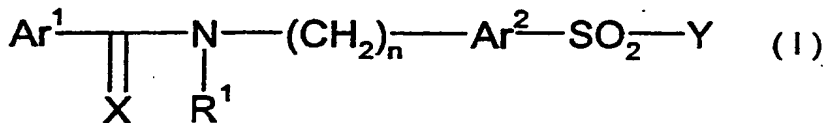
(75) Inventors/Applicants (*for US only*): ARKINSTALL,
Stephen [GB/FR]; La Bergerie/Les Goths, F-74350
Cruseilles (FR). HALAZY, Serge [FR/FR]; 3, allée des
Jonquilles, F-74100 Vétraz-Monthoux (FR). CHURCH,
Dennis [US/CH]; 4, chemin des Vignes, CH-1291 Com-
mugny (CH). CAMPS, Montserrat [ES/CH]; 7, chemin
du Pré-Colomb, CH-1290 Versoix (CH). RUECKLE,
Thomas [DE/CH]; 142A, route de St. Julien, CH-1228

Published:

— With international search report.

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: PHARMACEUTICALLY ACTIVE SULFONAMIDE DERIVATIVES



fonamide derivatives are efficient modulators of the JNK pathway, they are in particular efficient and selective inhibitors of JNK 2 and 3. The present invention is furthermore related to novel sulfonamide derivatives as well as to methods of their preparation. The compounds of formula (I) according to the present invention being suitable pharmaceutical agents are those wherein Ar¹ and Ar² are independently from each other substituted or unsubstituted aryl or heteroaryl groups, X is O or S, preferably O; R¹ is hydrogen or a C₁-C₆-alkyl group, or R¹ forms a substituted or unsubstituted 5-6-membered saturated or unsaturated ring with Ar¹; n is an integer from 0 to 5, preferably between 1-3 and most preferred 1; Y within formula (I) is an unsubstituted or a substituted 4-12-membered saturated cyclic or bicyclic alkyl containing at least one nitrogen atom, whereby one nitrogen atom within said ring is forming a bond with the sulfonyl group of formula (I) thus providing a sulfonamide.

(57) Abstract: The present invention is related to sulfonamide derivatives of formula (I) notably for use as pharmaceutically active compounds, as well as to pharmaceutical formulations containing such sulfonamide derivatives. Said sul-

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
 US Department of Commerce
 United States Patent and Trademark
 Office, PCT
 2011 South Clark Place Room
 CP2/5C24
 Arlington, VA 22202
 ETATS-UNIS D'AMERIQUE
 in its capacity as elected Office

Date of mailing (day/month/year) 28 June 2001 (28.06.01)	
International application No. PCT/IB00/01380	Applicant's or agent's file reference 10638 WO
International filing date (day/month/year) 28 September 2000 (28.09.00)	Priority date (day/month/year) 28 September 1999 (28.09.99)
Applicant ARKINSTALL, Stephen et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
 20 April 2001 (20.04.01)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).


The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Pascal Piriou Telephone No.: (41-22) 338.83.38
--	--

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 10638 WO		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) FOR FURTHER ACTION	
International application No. PCT/IB00/01380	International filing date (day/month/year) 28/09/2000	Priority date (day/month/year) 28/09/1999	
International Patent Classification (IPC) or national classification and IPC C07D409/12			
Applicant APPLIED RESEARCH SYSTEMS ARS HOLDING N.V. et al.			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of 1 sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input checked="" type="checkbox"/> Certain defects in the international application VIII <input type="checkbox"/> Certain observations on the international application 			
Date of submission of the demand 20/04/2001		Date of completion of this report 23.10.2001	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized officer Scruton-Evans, I Telephone No. +49 89 2399 8272	



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

10/070954
JC Rec'd PCT/PTG 13 MAR 2002

International application No. PCT/IB00/01380

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17):*)

Description, pages:

1-89 as originally filed

Claims, No.:

1 (part), 2 (part), as originally filed
3-22

1 (part), as received on 06/10/2001 with letter of 04/10/2001
2 (part)

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB00/01380

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-10,13-22(partly).

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-10,13-22(partly).

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 1-22
 No: Claims

Inventive step (IS) Yes: Claims 11,12



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/IB00/01380

	No:	Claims	1-10,13-22
Industrial applicability (IA)	Yes:	Claims	1-22
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

With regard to the patentability of the present application, it is to be noted that as only an incomplete search was carried out (see search report), so this report relates only to that part of the application that has been searched. It is considered to be of importance that all of the examples provided have a 2,5thienyl or 2,5-furyl for Ar₂, and nearly all have phenyl for Ar₁.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

- 1) The following documents cited in the Search Report are referred to in this communication;

D1: WO 97 30992 A (BRISTOL-MYERS SQUIBB CO.;USA) 28 August 1997 (1997-08-28)

D2: WO 97 45403 A (PHARMACIA & UPJOHN COMPANY;USA) 4 December 1997 (1997-12-04)

D3: WO 98 53814 A (MERCK & CO., INC.;USA) 3 December 1998 (1998-12-03)

D4: WO 99 16751 A (MERCK PATENT G.M.B.H.;GERMANY) 8 April 1999 (1999-04-08)

D5: WO 99 21859 A (GLAXO GROUP LTD ;GLENNON KIMBERLY CAROLINE (US); PEEL MICHAEL ROBE) 6 May 1999 (1999-05-06)

D6: KELLY J ET AL: 'Synthesis of isomeric 3-piperidinyl and 3-pyrrolidinyl benzo[5,6]cyclohepta[1,2-b]pyridines: sulfonamido derivatives as inhibitors of Ras prenylation' BIOORG. MED. CHEM. (BMECEP,09680896);1998; VOL.6 (6); PP.673-686, XP000881133 Schering-Plough Research Institute;Kenilworth; 07033; NJ; USA (US)

D7 WO9630017

- 2) With regard to the requirement for novelty (Article 33(2) of the PCT), the compounds disclosed in the documents D1-D4 and D6 are excluded from the compound claim of claim 1 and the first medical use claim of claim 2 (the correction of the proviso relating to D2 to cyclopent[f]isoindol from cyanopent[f]isoindole is accepted). For the second medical use claim 13, as none of the documents D1-D4 and D6 disclose such a use, this can also be considered to be novel. On page 36 of the description, the reason for the first two provisos in claim 1 is given, and it is assumed that such compounds are not active, as stated, as claim 2 does not include these provisos. Article 33(2) of the PCT thus appears to have been satisfied for that matter which has been searched.
- 4) With regard to the requirement for inventive step (Article 33(3) of the PCT), the only comments made are with respect to the actual matter searched. The problem underlying the present application is considered to have been the provision of novel compounds which modulate the JNK pathway. The solution provided by the Applicant is the examples

of the application, which have been representatively shown to indeed solve the problem. As the closest structural prior arts have no such activity, and D5 has a completely different structure, that the compounds prepared and tested should have such an activity can be considered to be non-obvious, but the Examining Division does not consider that the problem can be assessed for claim 1 in its entirety, and thus only claims 11, 12 can be considered at this stage to satisfy the requirements of Article 33(3) of the PCT, as only a reasonable generalisation over the examples provided and tested can be justified.

Re Item VII

Certain defects in the international application

The terms "substituted" used in the claims would have to be defined according to the description if a generic claim was filed.

The preferred and most preferred embodiments in the claims should be made the subject of dependent claims

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
5 April 2001 (05.04.2001)

PCT

(10) International Publication Number
WO 01/23378 A1

(51) International Patent Classification⁷: **C07D 409/12**,
333/34, 333/36, 413/12, 495/04, 471/04, 409/14, 405/12,
A61K 31/496, 31/445 // (C07D 495/04, 333:00, 221:00)

(21) International Application Number: **PCT/IB00/01380**

(22) International Filing Date:
28 September 2000 (28.09.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
99810869.0 28 September 1999 (28.09.1999) EP

(71) Applicant (for all designated States except US): **APPLIED RESEARCH SYSTEMS ARS HOLDING N.V.**
[NL/NL]; Pietermaai 15, Curacao (AN).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **ARKINSTALL**,
Stephen [GB/FR]; La Bergerie/Les Goths, F-74350
Cruseilles (FR). **HALAZY**, Serge [FR/FR]; 3, allée des
Jonquilles, F-74100 Vétraz-Monthoux (FR). **CHURCH**,
Dennis [US/CH]; 4, chemin des Vignes, CH-1291 Com-
mugny (CH). **CAMPS**, Montserrat [ES/CH]; 7, chemin
du Pré-Colomb, CH-1290 Versoix (CH). **RUECKLE**,
Thomas [DE/CH]; 142A, route de St. Julien, CH-1228

Plan-les-Ouates (CH). **GOTTELAND**, Jean-Pierre
[FR/FR]; 423, chemin des Crets, F-74160 Beaumont
(FR). **BIAMONTE**, Marco [US/CH]; 13, rue St. Joseph,
CH-1227 Carouge (CH).

(74) Agents: **MOINAS**, Michel et al.; Moinas Savoye &
Cronin, 42, rue Plantamour, CH-1201 Geneva (CH).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,
DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

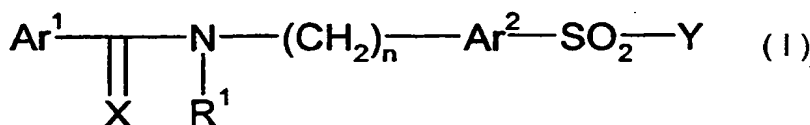
(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— With international search report.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PHARMACEUTICALLY ACTIVE SULFONAMIDE DERIVATIVES



fonamide derivatives are efficient modulators of the JNK pathway, they are in particular efficient and selective inhibitors of JNK 2 and 3. The present invention is furthermore related to novel sulfonamide derivatives as well as to methods of their preparation. The compounds of formula (I) according to the present invention being suitable pharmaceutical agents are those wherein Ar¹ and Ar² are independently from each other substituted or unsubstituted aryl or heteroaryl groups, X is O or S, preferably O; R¹ is hydrogen or a C₁-C₆-alkyl group, or R¹ forms a substituted or unsubstituted 5-6-membered saturated or unsaturated ring with Ar¹; n is an integer from 0 to 5, preferably between 1-3 and most preferred 1; Y within formula (I) is an unsubstituted or a substituted 4-12-membered saturated cyclic or bicyclic alkyl containing at least one nitrogen atom, whereby one nitrogen atom within said ring is forming a bond with the sulfonyl group of formula (I) thus providing a sulfonamide.

(57) Abstract: The present invention is related to sulfonamide derivatives of formula (I) notably for use as pharmaceutically active compounds, as well as to pharmaceutical formulations containing such sulfonamide derivatives. Said sul-

Pharmaceutically Active Sulfonamide Derivatives

Field of the invention

The present invention is related to sulfonamide derivatives for use as pharmaceutically active compounds, as well as pharmaceutical formulations containing such sulfonamide derivatives. In particular, the present invention is related to sulfonamide derivatives displaying a substantial modulatory, notably an inhibitory activity of the JNK (Jun-Kinase) function or pathways respectively, and which are therefore particularly useful in the treatment and/or prevention of disorders of the autoimmune and the neuronal system.

10 The present invention is furthermore related to novel sulfonamide derivatives as well as to methods of their preparation.

Background of the invention

Apoptosis denotes the complex contortions of the membrane and organelles of a cell as it undergoes the process of programmed cell death. During said process, the cell activates an intrinsic suicide program and systematically destroys itself. The following series of events can be observed :

- The cell surface begins to bleb and expresses pro-phagocytic signals. The whole apoptotic cell then fragments into membrane-bound vesicles that are rapidly and neatly disposed of by phagocytosis, so that there is minimal damage to the surrounding tissue.
- The cell then separates from its neighbors.

The nucleus also goes through a characteristic pattern of morphological changes as it commits genetic suicide, the chromatin condenses and is specifically cleaved to fragments of DNA.

25 Neuronal cell death plays an important role in ensuring that the nervous system develops normally. It appears that the death of developing neurons depends on the size of the target that they innervate: cells with fewer synaptic partners are more likely to die than those that have formed multiple synapses. This may reflect a process, which balances the relative number of pre- to postsynaptic neurons in the developing nervous system.

30 Although neuronal cell death was assumed to be apoptotic, it was only recently that

neurons in developing rodent brain were conclusively shown to undergo apoptosis as classified by morphology and DNA fragmentation. As cell death during development is clearly not a pathological process, it makes sense that cells actually cease to exist.

Neuronal death occurs via either apoptotic or necrotic processes following traumatic
5 nerve injury or during neurodegenerative diseases. Multiple components are emerging as key players having a role in driving neuronal programmed cell death. Amongst the components leading to neuronal apoptosis are members of the SAPK/JNK being a sub-family of MAP Kinases (MAPKs).

MAPKs (mitogen-activated protein kinases) are serine/threonine kinases that are acti-
10 vated by dual phosphorylation on threonine and tyrosine residues. In mammalian cells, there are at least three separate but parallel pathways that convey information generated by extra-cellular stimuli to the MAPKs. Said pathways consist of kinase cascades leading to activa-tion of the ERKs (extracellular regulated kinases), the JNKs (c-Jun N-terminal kinases), and the p38/CSBP kinases. While both the JNK and p38 pathways are
15 involved in relaying stress-type extramolecular signals, the ERK pathway is primarily responsible for transducing mitogenic/differentiation signals to the cell nucleus.

SAPK cascades represent a sub-family of the mitogen-activating protein kinase family, that are activated by different external stimuli including DNA damage following UV irradiation, TNF- α , IL-1 β , ceramide, cellular stress, and reactive oxygen species and
20 have distinct substrate specificities. Signal transduction via MKK4/JNK of MKK3/p38 results in the phosphorylation of inducible transcription factors, c-Jun and ATF2, which then act as either homodimers or heterodimers to initiate transcription of down-stream effectors.

c-Jun is a protein that is forming homodimers and heterodimers (with e.g. c-Fos) to pro-
25 duce the transactivating complex AP-which is required for the activation of many genes (e.g. matrix metalloproteinases) involved in the inflammatory response. The JNKs were discovered when it was found that several different stimuli such as UV light and TNF- α stimulated phosphorylation of c-Jun on specific serine residues in the N-terminus of the protein.

In a recent publication of Xie X et al, (*Structure* 1998, 6 (8); 983-991) it has been suggested that activation of stress-activated signal transduction pathways are required for neuronal apoptosis induced by NGF withdrawal in rat PC-12 and superior cervical ganglia (SCG) sympathetic neuronal cells. Inhibition of specific kinases, namely MAP kinase kinase 3 (MKK3) and MAP kinase kinase 4 (MKK4), or c-Jun (part of the MKK-4 cascade) may be sufficient to block apoptosis (see also Kumagai Y et al, in *Brain Res Mol Brain Res*, 1999, 67(1), 10-17 and Yang DD et al in *Nature*, 1997, 389 (6653); 865-870). Within a few hours of NGF deprivation in SCG neurones, c-Jun becomes highly phosphorylated and protein levels increase. Similarly in rat PC-12 cells deprived of NGF, JNK and p38 undergo sustained activation while ERKs are inhibited. Consistent with this JNK3 KO mice are resistant to excitotoxicity induced apoptosis in the hippocampus and more importantly they display greatly reduced epileptic like seizures in response to excitotoxicity as compared to normal animals (*Nature* 1997, 389, 865-870). More recently, it has been reported that the JNK signalling pathway is implicated in cell proliferation and could play an important role in autoimmune diseases (*Immunity*, 1998, 9, 575-585; *Current Biology*, 1999, 3, 116-125) which are mediated by T-cell activation and proliferation.

Naive (precursor) CD4⁺ helper T (Th) cells recognise specific MHC-peptide complexes on antigen-presenting cells (APC) via the T-cell receptor (TCR) complex. In addition to the TCR-mediated signal, a co-stimulatory signal is provided at least partially by the ligation of CD28 expressed on T-cells with B7 proteins on APC. The combination of these two signals induces T-cell clonal expression.

After 4-5 days of proliferation, precursor of CD4⁺ T cells differentiate into armed effector Th cells that mediate the functions of the immune system. During the differentiation process, substantial reprogramming of gene expression occurs.

Two subsets of effector Th cells have been defined on the basis of their distinct cytokine secretion pattern and their immuno-modulatory effects: Th1 cells produce IFN γ and LT (TNF- β), which are required for cell-mediated inflammatory reactions; Th2 cells secrete IL-4, IL-5, IL-6, IL-10 and IL-13, which mediate B cell activation and differentiation. These cells play a central role in the immune response. The JNK MAP Kinase pathway is induced in Th1 but not in Th2 effector cells upon antigen stimulation. Furthermore,

the differentiation of precursor CD4⁺ T cells into effector Th1 but not Th2 cells is impaired in JNK1 and JNK2-deficient mice. Therefore, in recent years it has been realised that the JNK kinase pathway plays an important role in the balance of Th1 and Th2 immune response through JNK1 and JNK2.

5 With the objective of inhibiting the JNK kinase pathway, WO/9849188 teaches the use of a human polypeptide, i.e. JNK-interacting protein 1 (JIP-1), which is a biological product and which has also been assayed for overcoming apoptosis related disorders. Although such human polypeptides have been confirmed to have an inhibitory effect onto the JNK kinase pathway, a whole variety of drawbacks are associated with their
10 use :

- Active bio-peptides or bio-proteins are only obtained by means of rather comprehensive and expensive biosynthesis which consequently frequently renders the resulting products fairly cost-intensive.
- The peptides are known to display poor membrane penetration and may not
15 cross the blood brain membrane,
- The principal drawback to the use of peptide inhibitors or antagonists is the problem of low oral bioavailability resulting from intestinal degradation. Hence, they must be administered parenterally and finally,
- peptide inhibitors or antagonists are frequently viewed by the host body as in-
20 truding material to be eliminated, thus setting off an auto-immune response.

Hence, it is an objective of the present invention to provide relatively small molecules that avoid essentially all of the above-mentioned drawbacks arising from the use of peptides or proteins, however, which are suitable for the treatment of a variety of diseases, in particular of neuronal or the autoimmune system related disorders. It is notably
25 an objective of the present invention to provide relatively small molecule chemical compounds which are able to modulate, preferably to down-regulate or to inhibit the JNK (Jun kinase) pathway so to be available as a convenient method of treating diseases which are preferably mediated by the JNK function. Moreover, it is an objective of the present invention to provide methods for preparing said small molecule chemical com-
30 pounds. It is furthermore an objective of the present invention to provide a new category of pharmaceutical formulations for the treatment of diseases, preferably mediated by the

JNK function. It is finally an objective of the present invention to provide a method for the treatment and/or prevention of diseases that are caused by disorders of the autoimmune and/or the neuronal system.

5 Description of the invention

The aforementioned objectives have been met according to the independent claims. Preferred embodiments are set out within the dependent claims which are incorporated herewith.

10 The following paragraphs provide definitions of the various chemical moieties and terms that make up the compounds according to the invention and are intended to apply uniformly throughout the specification and claims unless an otherwise expressly set out definition provides a broader definition.

15 “C₁-C₆-alkyl” refers to monovalent alkyl groups having 1 to 6 carbon atoms. This term is exemplified by groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-hexyl and the like.

“Aryl” refers to an unsaturated aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (e.g. phenyl) or multiple condensed rings (e.g. naphthyl). Preferred aryl include phenyl, naphthyl, phenantrenyl and the like.

20 “C₁-C₆-alkyl aryl” refers to C₁-C₆-alkyl groups having an aryl substituent, including benzyl, phenethyl and the like.

25 “Heteroaryl” refers to a monocyclic heteroaromatic, or a bicyclic or a tricyclic fused-ring heteroaromatic group. Particular examples of heteroaromatic groups include optionally substituted pyridyl, pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-triazinyl, 1,2,3-triazinyl, benzofuryl, [2,3-dihydro]benzofuryl, isobenzofuryl, benzothienyl, benzotriazolyl, isobenzothienyl, indolyl, isoindolyl, 3H-indolyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, quinoliziny, quinazolinyl, pthalazinyl, quinoxaliny, cinnolinyl, naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-

b]pyridyl, quinolyl, isoquinolyl, tetrazolyl, 5,6,7,8-tetrahydroquinolyl, 5,6,7,8-tetrahydroisoquinolyl, purinyl, pteridiny, carbazolyl, xanthenyl or benzoquinolyl.

“C₁-C₆-alkyl heteroaryl” refers to C₁-C₆-alkyl groups having a heteroaryl substituent, including 2-furylmethyl, 2-thienylmethyl, 2-(1H-indol-3-yl)ethyl and the like.

- 5 “Alkenyl” refers to alkenyl groups preferably having from 2 to 6 carbon atoms and having at least 1 or 2 sites of alkenyl unsaturation. Preferable alkenyl groups include ethenyl (-CH=CH₂), n-2-propenyl (allyl, -CH₂CH=CH₂) and the like.

- “Alkynyl” refers to alkynyl groups preferably having from 2 to 6 carbon atoms and having at least 1-2 sites of alkynyl unsaturation, preferred alkynyl groups include ethynyl (-C≡CH), propargyl (-CH₂C≡CH), and the like.
- 10

“Acyl” refers to the group -C(O)R where R includes “C₁-C₆-alkyl”, “aryl”, “heteroaryl”, “C₁-C₆-alkyl aryl” or “C₁-C₆-alkyl heteroaryl”.

“Acyloxy” refers to the group -OC(O)R where R includes “C₁-C₆-alkyl”, “aryl”, “heteroaryl”, “C₁-C₆-alkyl aryl” or “C₁-C₆-alkyl heteroaryl”.

- 15 “Alkoxy” refers to the group -O-R where R includes “C₁-C₆-alkyl” or “aryl” or “heteroaryl” or “C₁-C₆-alkyl aryl” or “C₁-C₆-alkyl heteroaryl”. Preferred alkoxy groups include by way of example, methoxy, ethoxy, phenoxy and the like.

“Alkoxycarbonyl” refers to the group -C(O)OR where R includes “C₁-C₆-alkyl” or “aryl” or “heteroaryl” or “C₁-C₆-alkyl aryl” or “C₁-C₆-alkyl heteroaryl”.

- 20 “Aminocarbonyl” refers to the group -C(O)NRR' where each R, R' includes independently hydrogen or C₁-C₆-alkyl or aryl or heteroaryl or “C₁-C₆-alkyl aryl” or “C₁-C₆-alkyl heteroaryl”.

- “Acylamino” refers to the group -NR(CO)R' where each R, R' is independently hydrogen or “C₁-C₆-alkyl” or “aryl” or “heteroaryl” or “C₁-C₆-alkyl aryl” or “C₁-C₆-alkyl heteroaryl”.
- 25

“Halogen” refers to fluoro, chloro, bromo and iodo atoms.

"Sulfonyl" refers to group " $-\text{SO}_2\text{-R}$ " wherein R is selected from H, "aryl", "heteroaryl", " $\text{C}_1\text{-C}_6\text{-alkyl}$ ", " $\text{C}_1\text{-C}_6\text{-alkyl}$ " substituted with halogens e.g. an $-\text{SO}_2\text{-CF}_3$ group, " $\text{C}_1\text{-C}_6\text{-alkyl aryl}$ " or " $\text{C}_1\text{-C}_6\text{-alkyl heteroaryl}$ ".

"Sulfoxy" refers to a group " $-\text{S}(\text{O})\text{-R}$ " wherein R is selected from H, " $\text{C}_1\text{-C}_6\text{-alkyl}$ ",
5 " $\text{C}_1\text{-C}_6\text{-alkyl}$ " substituted with halogens e.g. an $-\text{SO}\text{-CF}_3$ group, "aryl", "heteroaryl", " $\text{C}_1\text{-C}_6\text{-alkyl aryl}$ " or " $\text{C}_1\text{-C}_6\text{-alkyl heteroaryl}$ ".

"Thioalkoxy" refers to groups $-\text{S-R}$ where R includes " $\text{C}_1\text{-C}_6\text{-alkyl}$ " or "aryl" or "heteroaryl" or " $\text{C}_1\text{-C}_6\text{-alkyl aryl}$ " or " $\text{C}_1\text{-C}_6\text{-alkyl heteroaryl}$ ". Preferred thioalkoxy groups include thiomethoxy, thioethoxy, and the like.

10 "Substituted or unsubstituted" : Unless otherwise constrained by the definition of the individual substituent, the above set out groups, like "alkyl", "alkenyl", "alkynyl", "aryl" and "heteroaryl" etc. groups can optionally be substituted with from 1 to 5 substituents selected from the group consisting of " $\text{C}_1\text{-C}_6\text{-alkyl}$ ", " $\text{C}_1\text{-C}_6\text{-alkyl aryl}$ ", " $\text{C}_1\text{-C}_6\text{-alkyl heteroaryl}$ ", " $\text{C}_2\text{-C}_6\text{-alkenyl}$ ", " $\text{C}_2\text{-C}_6\text{-alkynyl}$ ", primary, secondary or tertiary
15 amino groups or quaternary ammonium moieties, "acyl", "acyloxy", "acylamino", "aminocarbonyl", "alkoxycarbonyl", "aryl", "heteroaryl", carboxyl, cyano, halogen, hydroxy, mercapto, nitro, sulfoxy, sulfonyl, alkoxy, thioalkoxy, trihalomethyl and the like. Alternatively said substitution could also comprise situations where neighboring substituents have undergone ring closure, notably when vicinal functional substituents are
20 involved, thus forming e.g. lactams, lactons, cyclic anhydrides, but also acetals, thioacetals, aminals formed by ring closure for instance in an effort to obtain a protective group.

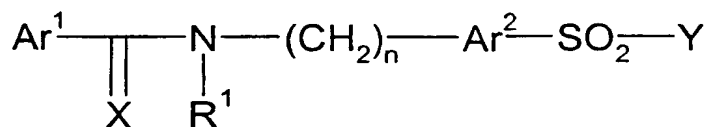
"Pharmaceutically acceptable salts or "complexes" refers to salts or complexes of the below-identified compounds of formula I that retain the desired biological activity. Examples of such salts include, but are not restricted to acid addition salts formed with inorganic acids (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, fumaric acid, maleic acid, ascorbic acid, benzoic acid, tannic acid, pantoic acid, alginic acid, polyglutamic acid, naphthalene sulfonic acid, naphthalene disulfonic acid, and polygalacturonic acid. Said compounds can
30

also be administered as pharmaceutically acceptable quaternary salts known by a person skilled in the art, which specifically include the quaternary ammonium salt of the formula $-NR,R',R''^+ Z^-$, wherein R, R', R'' is independently hydrogen, alkyl, or benzyl, and Z is a counterion, including chloride, bromide, iodide, -O-alkyl, toluenesulfonate, methylsulfonate, sulfonate, phosphate, or carboxylate (such as benzoate, succinate, acetate, glycolate, maleate, malate, fumarate, citrate, tartrate, ascorbate, cinnamate, mandelate, and diphenylacetate).

“Pharmaceutically active derivative” refers to any compound that upon administration to the recipient, is capable of providing directly or indirectly, the activity disclosed herein.

“Enantiomeric excess” (ee) refers to the products that are obtained by an essentially enantiomeric synthesis or a synthesis comprising an enantioselective step, whereby a surplus of one enantiomer in the order of at least about 52% ee is yielded. In the absence of an enantiomeric synthesis, racemic products are usually obtained that do however also have the inventive set out activity as JNK2 and/or 3 inhibitors.

Quite surprisingly, it was now found that sulfonamide derivatives according to formula I are suitable pharmaceutically active agents, by effectively modulating, in particular by down-regulating inhibiting the action of JNK's, notably of JNK 2 and/or 3.



I

The compounds of formula I according to the present invention being suitable pharmaceutical agents are those wherein

Ar¹ and Ar² are independently from each other substituted or unsubstituted aryl or heteroaryl groups,

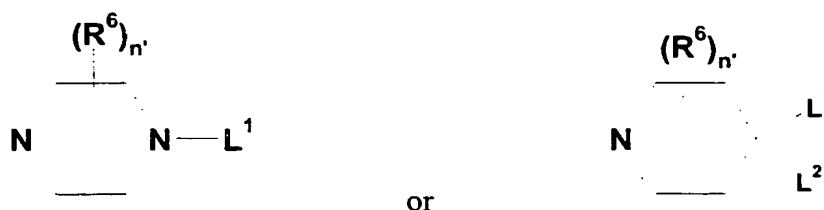
X is O or S, preferably O;

R¹ is hydrogen or a C₁-C₆-alkyl group, preferably H, or R¹ forms a substituted or unsubstituted 5-6-membered saturated or non-saturated ring with Ar¹;

n is an integer from 0 to 5, preferably between 1-3 and most preferred 1.

Y within formula I is an unsubstituted or a substituted 4-12-membered saturated cyclic or bicyclic alkyl containing at least one nitrogen atom, whereby one nitrogen atom within said ring is forming a bond with the sulfonyl group of formula I thus providing the sulfonamide.

- 5 In a preferred embodiment of the present invention, Y is a piperidine or piperazine moiety according to the below formula

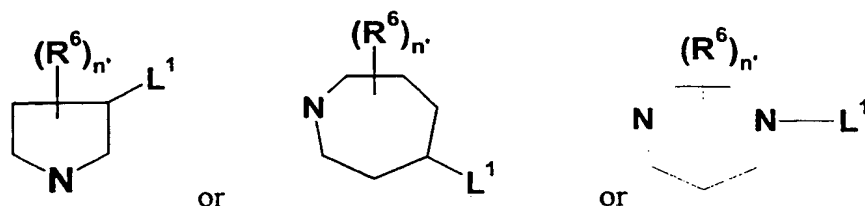


- In said piperidine or piperazine groups, L^1 and L^2 are independently selected from each other from the group comprising or consisting of H, substituted or unsubstituted C_1 - C_6 -alkyl, substituted or unsubstituted C_2 - C_6 -alkenyl, substituted or unsubstituted C_2 - C_6 -alkynyl, substituted or unsubstituted cyclic C_4 - C_8 -alkyl optionally containing 1-3 heteroatoms and optionally fused with aryl or heteroaryl; or L^1 and L^2 are independently selected from the group comprising or consisting of substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, aryl- C_1 - C_6 -alkyl, heteroaryl- C_1 - C_6 -alkyl, -C(O)-OR³, -C(O)-R³, -C(O)-NR^{3'}R³, -NR^{3'}R³, -NR^{3'}C(O)R³, -NR^{3'}C(O)NR^{3'}R³, -(SO)R³, -(SO₂)R³, -NSO₂R³, -SO₂NR^{3'}R³.

- Thereby, R³ and R^{3'} are substituents independently selected from the group comprising or consisting of H, substituted or unsubstituted C_1 - C_6 -alkyl, substituted or unsubstituted C_2 - C_6 -alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aryl- C_1 - C_6 -alkyl, substituted or unsubstituted heteroaryl- C_1 - C_6 -alkyl.

- R⁶ is selected from the group comprising or consisting of hydrogen, substituted or unsubstituted C_1 - C_6 -alkyl, substituted or unsubstituted C_1 - C_6 -alkoxy, OH, halogen, nitro, cyano, sulfonyl, oxo (=O), sulfoxy, acyloxy, thioalkoxy and n' is an integer from 0 to 4, preferably 1 or 2.

According to a further preferred embodiment of the present invention, Y is a pyrrolidine, an azepan or a 1,4-diazepan moiety of the below formulas



In said moieties, L^1 is selected from the group comprising or consisting of H, substituted or unsubstituted C_1 - C_6 -alkyl, substituted or unsubstituted C_2 - C_6 -alkenyl, substituted or unsubstituted C_2 - C_6 -alkynyl, substituted or unsubstituted cyclic C_4 - C_8 -alkyl optionally containing 1-3 heteroatoms and optionally fused with aryl or heteroaryl; or L^1 and L^2 are independently selected from the group comprising or consisting of substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, aryl- C_1 - C_6 -alkyl, heteroaryl- C_1 - C_6 -alkyl, $-C(O)-OR^3$, $-C(O)-R^3$, $-C(O)-NR^{3'}R^3$, $-NR^{3'}R^3$, $-NR^{3'}C(O)R^3$, $-NR^{3'}C(O)NR^{3'}R^3$, $-(SO)R^3$, $-(SO_2)R^3$, $-NSO_2R^3$, $-SO_2NR^{3'}R^3$.

Thereby, R^3 and $R^{3'}$ are substituents independently selected from the group comprising or consisting of H, substituted or unsubstituted C_1 - C_6 -alkyl, substituted or unsubstituted C_2 - C_6 -alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aryl- C_1 - C_6 -alkyl, substituted or unsubstituted heteroaryl- C_1 - C_6 -alkyl.

R^6 is selected from the group comprising or consisting of hydrogen, substituted or unsubstituted C_1 - C_6 -alkyl, substituted or unsubstituted C_1 - C_6 -alkoxy, OH, halogen, nitro, cyano, sulfonyl, oxo ($=O$), sulfoxy, acyloxy, thioalkoxy and n' is an integer from 0 to 4, preferably 0.

Most preferred azepan or a 1,4-diazepan moieties are those wherein, L^1 is $-NR^{3'}R^3$, with R^3 being hydrogen and $R^{3'}$ being a C_1 - C_{12} , preferably C_4 - C_6 -alkyl which is optionally substituted with cycloalkyl, aryl or heteroaryl group.

All of the above mentioned aryl or heteroaryl groups could optionally be substituted by at least one of the groups selected from substituted or unsubstituted C_1 - C_6 -alkyl, like trihalomethyl, substituted or unsubstituted C_1 - C_6 -alkoxy, acyloxy, substituted or unsub-

stituted C₂-C₆-alkenyl, substituted or unsubstituted C₂-C₆-alkynyl, amino, acylamino, aminocarbonyl, C₁-C₆-alkoxycarbonyl, aryl, carboxyl, cyano, halogen, hydroxy, nitro, sulfonyl, sulfoxy, C₁-C₆-thioalkoxy.

Also L¹ and L² taken together could form a 4-8-membered saturated cyclic alkyl or heteroalkyl group, like triazolines, tetrazolines, oxazolines, isoxazolines, oxazoles or isoxazoles. In a preferred embodiment L¹ and L² form together 5-6-membered saturated cyclic alkyl ring containing 2-3 nitrogen atoms.

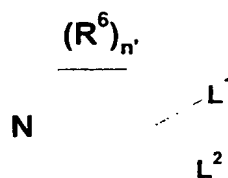
The present invention also includes the geometrical isomers, the optical active forms, enantiomers, diastereomers of compounds according to formula I, as well as their racemates and also pharmaceutically acceptable salts as well as the pharmaceutically active derivatives of the sulfonamide derivatives of formula I.

Preferred Ar¹ and Ar² in formula I are those that are independently selected from the group comprising or consisting of phenyl, thienyl, furanyl, pyridyl, optionally substituted by substituted or unsubstituted C₁-C₆-alkyl, like trihalomethyl, substituted or unsubstituted C₁-C₆-alkoxy, substituted or unsubstituted C₂-C₆-alkenyl, substituted or unsubstituted C₂-C₆-alkynyl, amino, acylamino, aminocarbonyl, C₁-C₆-alkoxycarbonyl, aryl, carboxyl, cyano, halo, hydroxy, nitro, sulfonyl, sulfoxy, acyloxy, C₁-C₆-thioalkoxy. The most preferred Ar¹ is a substituted phenyl, e.g. a 4-chlorophenyl, nitrophenyl, hydroxyphenyl, alkoxy phenyl, pyridyl, 3,4-dihydroxyphenyl, thioxo-dihydropyridine or its tautomer, pyrazole while the most preferred Ar² is an unsubstituted or substituted thienyl or furanyl group.

Where Ar¹ is a 4-chlorophenyl, nitrophenyl, hydroxyphenyl, alkoxy phenyl, pyridyl, 3,4-dihydroxyphenyl, thioxo-dihydropyridine or its tautomer, pyrazole group, X is preferably O, R¹ is hydrogen, n is 1 and Ar² is thienyl or furanyl.

A particularly preferred embodiment of the present invention is related to the sulfonamide derivatives, wherein Y is a substituted or unsubstituted piperidine residue,





whereby R^6 , n , L^1 and L^2 are as above defined.

In a more preferred embodiment of the sulfonamide derivatives according to formula I, Ar^1 is 4-chlorophenyl, X is O, R^1 is hydrogen, n is 1, Ar^2 is thienyl, Y is



whereby L^2 is H and L^1 is a 5-membered cyclic group containing 3 heteroatoms, preferably a triazole ring, being preferably fused with a substituted or unsubstituted aryl group, e.g. a benzotriazole; or L^2 is $-C(O)-R^3$, or $-NHR^3$.

Thereby, R^3 is a substituent selected from the group comprising or consisting of substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aryl- C_1 - C_6 -alkyl, substituted or unsubstituted heteroaryl- C_1 - C_6 -alkyl.

Said aryl or heteroaryl groups may optionally be substituted by halogen, hydroxy, nitro, sulfonyl, e.g. a trifluoromethylsulfonyl group.

Specific examples of compounds of formula I include the following :

4-chloro-*N*-[5-(piperazine-1-sulfonyl)-thiophen-2-yl-methyl]-benzamide

4-Chloro-*N*-{5-[4-(3-Trifluoromethanesulfonyl-phenylamino)-piperidine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-chloro-*N*-({5-[(4-pyridin-2-ylpiperazin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

4-chloro-*N*-[(5-{[4-(4-fluorobenzoyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide

4-chloro-*N*-{[5-({4-[4-(trifluoromethyl)phenyl]piperazin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide

4-chloro-*N*-({5-[(4-{2-nitrophenyl}piperazin-1-yl)sulfonyl]thien-2-yl}methyl)-

benzamide



- 4-chloro-N-({5-[(4-{4-nitrophenyl})piperazin-1-yl]sulfonyl}thien-2-yl)methyl)-benzamide
- 4-chloro-N-({5-[(4-(2-furoyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl}benzamide
- 4-chloro-N-({5-[(4-(4-hydroxyphenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl)-benzamide
- 5 4-chloro-N-({5-[(4-(2-oxo-2-pyrrolidin-1-ylethyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl)-benzamide
- 4-chloro-N-({5-[(4-(2-morpholin-4-yl-2-oxoethyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl}benzamide
- 10 4-chloro-N-({5-[(4-(pyridin-4-ylmethyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl)-benzamide
- 4-chloro-N-({5-[(4-(2-thien-2-ylethyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl)-benzamide
- 4-chloro-N-({5-[(4-(3,5-dimethoxyphenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl)-benzamide
- 15 4-chloro-N-({5-[(4-(cyclohexylmethyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl)-benzamide
- 4-chloro-N-({5-[(4-(2-methoxyphenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl)-benzamide
- 20 N-({5-[(4-benzylpiperazin-1-yl]sulfonyl}thien-2-yl)methyl)-4-chlorobenzamide
- 4-chloro-N-({5-[(4-(2-phenylethyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl)-benzamide
- 4-chloro-N-({5-[(4-(4-fluorobenzyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl)-benzamide
- 25 4-chloro-N-({5-[(4-(2-cyanophenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl)-benzamide
- 4-chloro-N-({5-[(4-{4-chloro-3-(trifluoromethyl)phenyl}piperazin-1-yl]sulfonyl}thien-2-yl)methyl}benzamide
- 4-chloro-N-({5-[(4-(3-piperidin-1-ylpropyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl)-benzamide
- 30 4-chloro-N-({5-[(4-{4-chloro-2-nitrophenyl}piperazin-1-yl]sulfonyl}thien-2-yl)methyl}benzamide



- 4-chloro-N-[(5-{[4-(6-methylpyridin-2-yl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide
- 4-chloro-N-({5-[(4-hydroxy-4-phenylpiperidin-1-yl)sulfonyl]thien-2-yl}methyl)-benzamide
- 5 N-({5-[(4-benzoylpiperidin-1-yl)sulfonyl]thien-2-yl}methyl)-4-chlorobenzamide
- 4-chloro-N-[(5-{[4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- N-({5-[(4-benzylpiperidin-1-yl)sulfonyl]thien-2-yl}methyl)-4-chlorobenzamide
- 4-chloro-N-({5-[(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-8-yl)sulfonyl]thien-2-yl}methyl)benzamide
- 10 4-chloro-N-{{5-({4-[2-(methylanilino)-2-oxoethyl]piperazin-1-yl}sulfonyl)thien-2-yl}methyl}benzamide
- 4-chloro-N-{{5-({4-[hydroxy(diphenyl)methyl]piperidin-1-yl}sulfonyl)thien-2-yl}methyl}benzamide
- 15 4-chloro-N-[(5-{[4-(3-cyanopyrazin-2-yl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide
- 4-chloro-N-({5-[(4-{5-nitropyridin-2-yl}piperazin-1-yl)sulfonyl]thien-2-yl}methyl)-benzamide
- 4-chloro-N-{{5-({4-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}sulfonyl)thien-2-yl}methyl}benzamide
- 20 4-chloro-N-{{5-({4-[5-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}sulfonyl)thien-2-yl}methyl}benzamide
- 4-chloro-N-{{5-({4-[3-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}sulfonyl)thien-2-yl}methyl}benzamide
- 25 4-chloro-N-[(5-{[4-(2,4-difluorobenzoyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide
- methyl 5-{4-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperazin-1-yl}-7-(trifluoromethyl)thieno[3,2-b]pyridine-3-carboxylate
- ethyl 2-{4-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperazin-1-yl}-5-cyano-6-methylnicotinate
- 30 4-chloro-N-{{5-({4-[5-cyano-4,6-bis(dimethylamino)pyridin-2-yl]piperazin-1-yl}sulfonyl)thien-2-yl}methyl}benzamide



- 4-chloro-N- {[5-({4-[6-methyl-2-(trifluoromethyl)quinolin-4-yl]piperazin-1-yl} sulfonyl)thien-2-yl)methyl} benzamide
- tert-butyl 4-[(5-{[(4-chlorobenzoyl)amino]methyl} thien-2-yl)sulfonyl]piperazine-1-carboxylate
- 5 2-{4-[(5-{[(4-chlorobenzoyl)amino]methyl} thien-2-yl)sulfonyl]piperazin-1-yl}-8-ethyl-5-oxo-5,8-dihydropyrido[2,3-d]pyrimidine-6-carboxylic acid
- 7-{4-[(5-{[(4-chlorobenzoyl)amino]methyl} thien-2-yl)sulfonyl]piperazin-1-yl}-1-ethyl-6-fluoro-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylic acid
- 7-{4-[(5-{[(4-chlorobenzoyl)amino]methyl} thien-2-yl)sulfonyl]piperazin-1-yl}-1-ethyl-10 6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid
- 4-chloro-N-[(5-{[4-(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]piperazin-1-yl}sulfonyl)thien-2-yl)methyl]benzamide
- 4-chloro-N- {[5-({4-[(2E)-3-phenylprop-2-enyl]piperazin-1-yl} sulfonyl)thien-2-yl)methyl} benzamide
- 15 4-chloro-N-[(5-{[4-(3-phenylpropyl)piperazin-1-yl]sulfonyl} thien-2-yl)methyl]-benzamide
- 4-chloro-N-[(5-{[4-(3,4,5-trimethoxyphenyl)piperazin-1-yl]sulfonyl} thien-2-yl)-methyl]benzamide
- N-[(5-{[4-(4-tert-butylbenzyl)piperazin-1-yl]sulfonyl} thien-2-yl)methyl]-4-chloro-20 benzamide
- 4-chloro-N-[(5-{[4-(4-fluorophenyl)piperazin-1-yl]sulfonyl} thien-2-yl)methyl]-benzamide
- 4-chloro-N-[(5-{[4-(2-hydroxyphenyl)piperazin-1-yl]sulfonyl} thien-2-yl)methyl]-benzamide
- 25 4-chloro-N- {[5-({4-[4-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl} sulfonyl)thien-2-yl)methyl} benzamide
- 4-chloro-N-[(5-{[4-(5-cyanopyridin-2-yl)piperazin-1-yl]sulfonyl} thien-2-yl)methyl]-benzamide
- tert-butyl 1-[(5-{[(4-chlorobenzoyl)amino]methyl} thien-2-yl)sulfonyl]piperidin-4-ylcarbamate
- 30 4-chloro-N-({5-[(4-phenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl)benzamide
- 4-chloro-N- {[5-(piperidin-1-ylsulfonyl)thien-2-yl)methyl} benzamide



- 4-chloro-N-[(5-{[4-(1-naphthyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 4-chloro-N-[(5-{[4-(3,4-dichlorophenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide
- 4-chloro-N-[(5-{[4-(3-(trifluoromethyl)phenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 5 4-chloro-N-[(5-{[3-(3-hydroxy-4-[3-(trifluoromethyl)phenyl]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 4-chloro-N-[(5-{[4-(2-methylphenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide
- 10 N-[(5-{[(1R,4R)-5-benzyl-2,5-diazabicyclo[2.2.1]hept-2-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide
- N-[(5-{[4-(benzyloxy)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide
- 4-chloro-N-[(5-{[4-(2-chlorodibenzo[b,f][1,4]oxazepin-11-yl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 15 N-(4-chlorophenyl)-2-(5-{[4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)acetamide
- 4-chloro-N-[(5-{[4-(4-hydroxypiperidin-1-yl)sulfonyl]thien-2-yl)methyl]benzamide
- N-[(5-{[4-(4-acetylphenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide
- 20 4-chloro-N-[(5-{[4-(3,5-dichloropyridin-4-yl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 4-chloro-N-[(5-{[4-(3-methoxyphenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide
- N-[(5-{[4-(4-benzyl-4-hydroxypiperidin-1-yl)sulfonyl]thien-2-yl)methyl]-4-chlorobenzamide
- 25 4-chloro-N-[(5-{[4-(2-tert-butyl-1H-indol-5-yl)amino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide
- 4-chloro-N-[(5-{[4-[(phenylacetyl)amino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 30 4-chloro-N-[(5-{[4-(tetrahydrofuran-2-ylcarbonyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide



- 4-chloro-N-[(5-{[4-(6-chloropyridin-2-yl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide
- 4-chloro-N-[(5-{[4-(4-chlorophenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide
- 5 N-[(5-{[4-(2H-1,2,3-benzotriazol-2-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide
- 4-chloro-N-[(5-{[4-(4-chlorobenzoyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide
- 4-chloro-N-({5-[(4-phenoxy)piperidin-1-yl]sulfonyl}thien-2-yl)methyl)benzamide
- 10 N-({5-({4-[benzyl(methyl)amino]piperidin-1-yl}sulfonyl)thien-2-yl)methyl}-4-chlorobenzamide
- 4-chloro-N-({5-({4-[3-(2,4-dichlorophenyl)-1H-pyrazol-5-yl]piperidin-1-yl}sulfonyl)thien-2-yl)methyl}benzamide
- 4-chloro-N-[(5-{[4-(5-thien-2-yl-1H-pyrazol-3-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 15 4-chloro-N-[(5-{[4-(2,3,4,5,6-pentamethylbenzoyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 4-chloro-N-[(5-{[4-(phenylacetyl)-1,4-diazepan-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide
- 20 4-chloro-N-({5-({4-[5-(4-methoxyphenyl)-1H-pyrazol-3-yl]piperidin-1-yl}sulfonyl)thien-2-yl)methyl}benzamide
- N-({5-[(4-anilinopiperidin-1-yl)sulfonyl]thien-2-yl)methyl)-4-chlorobenzamide
- 4-chloro-N-[(5-{[4-(3-phenyl-1,2,4-thiadiazol-5-yl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 25 4-chloro-N-[(5-{[4-(2-phenylethyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide
- 4-chloro-N-({5-[(4-heptylpiperazin-1-yl)sulfonyl]thien-2-yl)methyl)benzamide
- 4-chloro-N-({5-[(4-octylpiperazin-1-yl)sulfonyl]thien-2-yl)methyl)benzamide
- N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-
- 30 chlorobenzamide
- 2-(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)-N-(4-chlorophenyl)acetamide



- 2-{1-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperidin-4-yl}-2H-1,2,3-benzotriazole-5-carboxylic
4-chloro-N-[(5-{[4-(5-chloro-1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 5 methyl 1-{1-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperidin-4-yl}-1H-1,2,3-benzotriazole-5-carboxylate
methyl 1-{1-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperidin-4-yl}-1H-1,2,3-benzotriazole-6-carboxylate
methyl 2-{1-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperidin-4-yl}-2H-1,2,3-benzotriazole-5-carboxylate
- 10 4-chloro-N-[(5-{[4-(6-chloro-1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
4-chloro-N-{[5-{[4-[5-(trifluoromethyl)-1H-1,2,3-benzotriazol-1-yl]piperidin-1-yl]sulfonyl}thien-2-yl)methyl}benzamide
- 15 N-[(5-{[4-(7-aza-1H-benzimidazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide
1-{1-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperidin-4-yl}-1H-1,2,3-benzotriazole-5-carboxylic
1-{1-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperidin-4-yl}-1H-1,2,3-benzotriazole-6-carboxylic
- 20 N-[(5-{[4-(2-amino-9H-purin-9-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide
4-chloro-N-[(5-{[4-(9H-purin-9-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide
- 25 N-[(5-{[4-(6-amino-9H-purin-9-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide
4-chloro-N-({5-[4-{6-nitro-1H-benzimidazol-1-yl}piperidin-1-yl]sulfonyl}thien-2-yl)methyl)benzamide
4-chloro-N-({5-[4-{5-nitro-1H-benzimidazol-1-yl}piperidin-1-yl]sulfonyl}thien-2-yl)methyl)benzamide
- 30 4-chloro-N-[(5-{[4-(2H-1,2,3-triazol-2-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide



- N-[(5-{[4-(1H-benzimidazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide
- 4-chloro-N-{[5-(4-[3-propylanilino]piperidin-1-yl)sulfonyl]thien-2-yl)methyl}-benzamide
- 5 4-chloro-N-{[5-(4-[3-(trifluoromethyl)anilino]piperidin-1-yl)sulfonyl]thien-2-yl)methyl}benzamide
- 4-chloro-N-{[5-(4-[3-(dimethylamino)anilino]piperidin-1-yl)sulfonyl]thien-2-yl)methyl}benzamide
- methyl
- 10 4-chloro-N-{[5-(4-[3-(methylsulfonyl)anilino]piperidin-1-yl)sulfonyl]thien-2-yl)methyl}benzamide
- 4-chloro-N-({5-[(4-{3-nitroanilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-benzamide
- 4-chloro-N-[(5-{[4-(2-methoxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide
- 15 3-({1-[(5-{[4-(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperidin-4-yl}amino)benzamide
- 4-chloro-N-{[5-(4-[2-(trifluoromethyl)anilino]piperidin-1-yl)sulfonyl]thien-2-yl)methyl}benzamide
- 20 4-chloro-N-({5-[(4-{2-nitro-4-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide
- 4-chloro-N-[(5-{[4-(4-chloroanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide
- 4-chloro-N-{[5-(4-[4-(trifluoromethyl)anilino]piperidin-1-yl)sulfonyl]thien-2-yl}-methyl}benzamide
- 25 4-chloro-N-({5-[(4-{4-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide
- 4-chloro-N-({5-[(4-{2-nitroanilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-benzamide
- 30 N-{[5-(4-[4-(aminocarbonyl)anilino]piperidin-1-yl)sulfonyl]thien-2-yl)methyl}-4-chlorobenzamide



- 4-chloro-N-{{5-({4-[4-(1,3-dithiolan-2-yl)anilino]piperidin-1-yl} sulfonyl)thien-2-yl}methyl}benzamide
- N-[(5-{{4-(3-chloroanilino)piperidin-1-yl} sulfonyl} thien-2-yl)methyl]-3-nitrobenzamide
- 5 4-chloro-N-[(5-{{4-(3-chloroanilino)piperidin-1-yl} sulfonyl} thien-2-yl)methyl]-benzamide
- 4-chloro-N-[(5-{{4-(3-methoxyanilino)piperidin-1-yl} sulfonyl} thien-2-yl)methyl]-benzamide
- 4-chloro-N-{{5-({4-[3-(methylsulfonyl)anilino]piperidin-1-yl} sulfonyl)thien-2-yl}methyl}benzamide
- 10 N-({5-[(4-{3-[amino(imino)methyl]anilino} piperidin-1-yl)sulfonyl]thien-2-yl} methyl)-4-chlorobenzamide
- 4-chloro-N-({5-[(4-{3-[(2-hydroxyethyl)sulfonyl]anilino} piperidin-1-yl)sulfonyl]thien-2-yl} methyl)benzamide
- 15 N-[(5-{{4-(2-aminoanilino)piperidin-1-yl} sulfonyl} thien-2-yl)methyl]-4-chlorobenzamide
- 4-chloro-N-[(5-{{4-(2-hydroxyanilino)piperidin-1-yl} sulfonyl} thien-2-yl)methyl]-benzamide
- 4-chloro-N-[(5-{{4-(4-hydroxyanilino)piperidin-1-yl} sulfonyl} thien-2-yl)methyl]-benzamide
- 20 4-chloro-N-({5-[(4-{3-[(trifluoromethyl)sulfanyl]anilino} piperidin-1-yl)sulfonyl]thien-2-yl} methyl)benzamide
- 4-chloro-N-[(5-{{4-(3-toluidino)piperidin-1-yl} sulfonyl} thien-2-yl)methyl]benzamide
- 4-chloro-N-({5-[(4-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]amino} piperidin-1-yl)sulfonyl]thien-2-yl} methyl)benzamide
- 25 4-chloro-N-{{5-({4-[3-(1,3-oxazol-5-yl)anilino]piperidin-1-yl} sulfonyl)thien-2-yl}methyl}benzamide
- N-[(5-{{4-(3-tert-butylanilino)piperidin-1-yl} sulfonyl} thien-2-yl)methyl]-4-chlorobenzamide
- 30 4-chloro-N-[(5-{{4-(2-propylanilino)piperidin-1-yl} sulfonyl} thien-2-yl)methyl]-benzamide



- 4-chloro-N-{{5-({4-[(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)amino]piperidin-1-yl} sulfonyl)thien-2-yl)methyl} benzamide
- 4-chloro-N-[(5-{{4-(2,3-dihydro-1H-inden-5-ylamino)piperidin-1-yl} sulfonyl} thien-2-yl)methyl] benzamide
- 5 4-chloro-N-[(5-{{4-(4-propylanilino)piperidin-1-yl} sulfonyl} thien-2-yl)methyl]-benzamide
- 4-chloro-N-[(5-{{4-({3-nitropyridin-2-yl} amino)piperidin-1-yl} sulfonyl} thien-2-yl)methyl] benzamide
- N-{{5-({4-[(3-aminopyridin-2-yl)amino]piperidin-1-yl} sulfonyl)thien-2-yl)methyl}-4-chlorobenzamide
- 10 N-[(5-{{4-([1,1'-biphenyl]-3-ylamino)piperidin-1-yl} sulfonyl} thien-2-yl)methyl]-4-chlorobenzamide
- N-[(5-{{4-(3-benzylanilino)piperidin-1-yl} sulfonyl} thien-2-yl)methyl]-4-chlorobenzamide
- 15 4-chloro-N-[(5-{{4-(pyrimidin-2-ylamino)piperidin-1-yl} sulfonyl} thien-2-yl)methyl]-benzamide
- 4-chloro-N-{{5-({4-[(4-(morpholin-4-yl)sulfonyl]anilino)piperidin-1-yl} sulfonyl)thien-2-yl)methyl} benzamide
- 4-chloro-N-({5-[(4-{{4-(trifluoromethyl)pyrimidin-2-yl} amino)piperidin-1-yl} sulfonyl]thien-2-yl)methyl} benzamide
- 20 4-chloro-N-[(5-{{4-(3-cyclohexyl-4-hydroxyanilino)piperidin-1-yl} sulfonyl} thien-2-yl)methyl] benzamide
- N-({5-[(4-{{3-[(butylamino)sulfonyl]anilino} piperidin-1-yl} sulfonyl)thien-2-yl} methyl)-4-chlorobenzamide
- 25 4-chloro-N-[(5-{{4-(3-ethylanilino)piperidin-1-yl} sulfonyl} thien-2-yl)methyl]-benzamide
- 4-chloro-N-[(5-{{4-(5,6,7,8-tetrahydronaphthalen-1-ylamino)piperidin-1-yl} sulfonyl} thien-2-yl)methyl] benzamide
- N-{{5-({4-[(3-aminosulfonyl)anilino]piperidin-1-yl} sulfonyl)thien-2-yl)methyl}-4-chlorobenzamide
- 30 4-chloro-N-[(5-{{4-(quinolin-5-ylamino)piperidin-1-yl} sulfonyl} thien-2-yl)methyl]-benzamide



- 4-chloro-N-[(5-{[4-(quinolin-8-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide
- 4-Chloro-N-[(5-{[4-(3-propylphenoxy)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide
- 5 4-chloro-N-{[5-(4-{(2E)-3-phenylprop-2-enoyl}piperazin-1-yl)sulfonyl]thien-2-yl)methyl}benzamide
- 4-chloro-N-({5-[4-{4-nitrobenzoyl}piperazin-1-yl)sulfonyl]thien-2-yl}methyl)-benzamide
- N-({5-[4-benzoylpiperazin-1-yl)sulfonyl]thien-2-yl}methyl)-4-chlorobenzamide
- 10 4-chloro-N-{[5-(4-[4-(trifluoromethyl)benzoyl]piperazin-1-yl)sulfonyl]thien-2-yl)methyl}benzamide
- 4-chloro-N-{[5-(4-[4-(dimethylamino)benzoyl]piperazin-1-yl)sulfonyl]thien-2-yl)methyl}benzamide
- 4-chloro-N-[(5-{[4-(2-fluorobenzoyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide
- 15 4-chloro-N-[(5-{[4-(2,6-difluorobenzoyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide
- 4-chloro-N-[(5-{[4-(3-fluorobenzoyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide
- 20 4-chloro-N-[(5-{[4-(2-naphthoyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 4-chloro-N-[(5-{[4-(1-naphthoyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 4-chloro-N-({5-[4-{2-nitrobenzoyl}piperazin-1-yl)sulfonyl]thien-2-yl}methyl)-benzamide
- 4-chloro-N-[(5-{[4-(pyridin-3-ylcarbonyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide
- 25 N-[(5-{[4-(2,1,3-benzoxadiazol-5-ylcarbonyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide
- 4-chloro-N-[(5-{[4-(2,4-difluorobenzoyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide
- 30 4-chloro-N-[(5-{[4-(2,4,6-trifluorobenzoyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide



- 4-chloro-N-[(5-{[4-(2,6-dichlorobenzoyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide
- 4-chloro-N-({5-[(4-heptanoylpiperazin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide
- 4-chloro-N-[(5-{[4-(quinolin-8-ylsulfonyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide
- 5 4-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide
- N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide
- 10 4-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide
- N-[(5-{[4-(2,4-difluorobenzoyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide
- N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide
- 15 N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide
- 4-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide
- 20 N-[(5-{[4-(2,4-difluorobenzoyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide
- N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide
- 3-nitro-N-[(5-{[4-(3-methoxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide
- 25 3-nitro-N-{{5-({4-[3-(trifluoromethyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl}-methyl}benzamide
- N-{{5-({4-[3-(dimethylamino)anilino]piperidin-1-yl}sulfonyl)thien-2-yl}methyl}-3-nitrobenzamide
- 30 3-nitro-N-{{5-({4-[3-(methylsulfonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl}-methyl}benzamide

- 3-nitro-N-{{5-({4-[3-(methylsulfonyl)anilino]piperidin-1-yl} sulfonyl)thien-2-yl}-methyl} benzamide
- N-{{5-({4-[3-(aminosulfonyl)anilino]piperidin-1-yl} sulfonyl)thien-2-yl}methyl}-3-nitrobenzamide
- 5 methyl
- N-{{5-({4-[3-(aminocarbonyl)anilino]piperidin-1-yl} sulfonyl)thien-2-yl}methyl}-3-nitrobenzamide
- 3-nitro-N-({5-({4-[3-nitroanilino]piperidin-1-yl} sulfonyl)thien-2-yl} methyl) benzamide
- 3-nitro-N-[(5-{{4-[2-methoxyanilino]piperidin-1-yl} sulfonyl} thien-2-yl)methyl]-
- 10 benzamide
- 3-nitro-N-{{5-({4-[2-(trifluoromethyl)anilino]piperidin-1-yl} sulfonyl)thien-2-yl}-methyl} benzamide
- 3-nitro-N-({5-{{4-[2-nitroanilino]piperidin-1-yl} sulfonyl} thien-2-yl} methyl) benzamide
- N-[(5-{{4-[4-chloroanilino]piperidin-1-yl} sulfonyl} thien-2-yl)methyl]-3-nitro-
- 15 benzamide
- 3-nitro-N-{{5-({4-[4-(trifluoromethyl)anilino]piperidin-1-yl} sulfonyl)thien-2-yl}-methyl} benzamide
- 3-nitro-N-({5-{{4-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl} sulfonyl)thien-2-yl} methyl) benzamide
- 20 N-{{5-({4-[4-(aminocarbonyl)anilino]piperidin-1-yl} sulfonyl)thien-2-yl}methyl}-3-nitrobenzamide
- N-[(5-{{4-[3-propylanilino]piperidin-1-yl} sulfonyl} thien-2-yl)methyl]-3-nitrobenzamide
- N-[(5-{{4-[3-chloroanilino]piperidin-1-yl} sulfonyl} thien-2-yl)methyl]-4-nitro-
- 25 benzamide
- 4-nitro-N-[(5-{{4-[3-methoxyanilino]piperidin-1-yl} sulfonyl} thien-2-yl)methyl]-benzamide
- 4-nitro-N-{{5-({4-[3-(trifluoromethyl)anilino]piperidin-1-yl} sulfonyl)thien-2-yl}-methyl} benzamide
- 30 N-{{5-({4-[3-(dimethylamino)anilino]piperidin-1-yl} sulfonyl)thien-2-yl}methyl}-4-nitrobenzamide



- 4-nitro-N-[(5-{[4-(3-propylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide
- 4-nitro-N-[(5-{[4-[3-(methylsulfonyl)anilino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 5 4-nitro-N-[(5-{[4-[3-(methylsulfonyl)anilino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- N-[(5-{[4-[3-(aminosulfonyl)anilino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide
- methyl
- 10 3-{[1-({5-[(4-nitrobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperidin-4-yl}amino}-benzamide
- 4-nitro-N-[(5-{[4-[3-nitroanilino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 4-nitro-N-[(5-{[4-(2-methoxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide
- 15 4-nitro-N-[(5-{[4-[2-(trifluoromethyl)anilino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 4-nitro-N-[(5-{[4-[2-nitroanilino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- N-[(5-{[4-(4-chloroanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide
- 20 4-nitro-N-[(5-{[4-[4-(trifluoromethyl)anilino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 4-nitro-N-[(5-{[4-[4-(trifluoromethyl)sulfonyl]anilino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- N-[(5-{[4-[4-(aminocarbonyl)anilino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide
- 25 nitrobenzamide
- N-[(5-{[4-[4-(1,3-dithiolan-2-yl)anilino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide
- N-[(5-{[4-[3-[amino(imino)methyl]anilino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide
- 30 N-[(5-{[4-[3-[(2-hydroxyethyl)sulfonyl]anilino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide
- N-[(5-{[4-anilinopiperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide

- N-({5-[(4-{3-[(2-hydroxyethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-4-nitrobenzamide
- N-({5-[(4-anilino)piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-4-nitrobenzamide
- N-({5-[(4-{3-[amino(imino)methyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-
5 4-nitrobenzamide
- 3-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide
- 4-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide
- 10 3-nitro-N-[(5-{[4-({3-nitropyridin-2-yl}amino)piperidin-1-yl)sulfonyl]thien-2-yl)-methyl]benzamide
- N-{{5-({4-[(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)amino]piperidin-1-yl}-sulfonyl)thien-2-yl}methyl}-3-nitrobenzamide
- N-[(5-{[4-(2,3-dihydro-1H-inden-5-ylamino)piperidin-1-yl)sulfonyl]thien-2-yl)-
15 methyl]-3-nitrobenzamide
- 3-nitro-N-[(5-{[4-(2-propylanilino)piperidin-1-yl)sulfonyl]thien-2-yl)methyl]-benzamide
- 3-nitro-N-[(5-{[4-(4-propylanilino)piperidin-1-yl)sulfonyl]thien-2-yl)methyl]-benzamide
- 20 N-[(5-{[4-(3-tert-butylanilino)piperidin-1-yl)sulfonyl]thien-2-yl)methyl]-3-nitrobenzamide
- 3-nitro-N-{{5-({4-[3-(1,3-oxazol-5-yl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl}methyl}benzamide
- 3-nitro-N-[(5-{[4-(2-phenylethyl)piperidin-1-yl)sulfonyl]thien-2-yl)methyl]benzamide
- 25 N-({5-[(4-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]amino}piperidin-1-yl)sulfonyl]-thien-2-yl}methyl)-3-nitrobenzamide
- N-[(5-{[4-([1,1'-biphenyl]-3-ylamino)piperidin-1-yl)sulfonyl]thien-2-yl)methyl]-3-nitrobenzamide
- N-[(5-{[4-(3-benzylanilino)piperidin-1-yl)sulfonyl]thien-2-yl)methyl]-3-nitro-
30 benzamide
- 3-nitro-N-{{5-({4-[3-(morpholin-4-ylsulfonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl}methyl}benzamide



- 3-nitro-N-[(5-{[4-(3-propylphenoxy)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 4-nitro-N-[(5-{[4-(pyrimidin-2-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide
- 5 N-{[5-(4-{[3-aminopyridin-2-yl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl}-4-nitrobenzamide
- 4-nitro-N-[(5-{[4-(3-nitropyridin-2-yl)amino]piperidin-1-yl}sulfonyl}thien-2-yl)-methyl]benzamide
- N-[(5-{[4-(2,3-dihydro-1H-inden-5-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)-methyl]-4-nitrobenzamide
- 10 4-nitro-N-[(5-{[4-(2-propylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide
- 4-nitro-N-[(5-{[4-(4-propylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide
- 15 N-[(5-{[4-(3-tert-butylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide
- 4-nitro-N-{[5-(4-{[3-(1,3-oxazol-5-yl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
- 4-nitro-N-[(5-{[4-(2-phenylethyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 20 N-({5-[(4-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-4-nitrobenzamide
- N-[(5-{[4-([1,1'-biphenyl]-3-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide
- N-[(5-{[4-(3-benzylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide
- 25 4-nitro-N-{[5-(4-{[3-(morpholin-4-ylsulfonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
- N-[(5-{[4-(2-aminoanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide
- 3-nitro-N-[(5-{[4-(pyrimidin-2-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide
- 30 N-{[5-(4-{[3-aminopyridin-2-yl]amino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl}-3-nitrobenzamide

- N-({5-[(4-{2-nitro-4-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl)methyl}-3-methoxybenzamide
3-nitro-N-[(5-{[4-(3-phenylpropyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide
- 5 3-nitro-N-({5-[(4-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}piperidin-1-yl)sulfonyl]thien-2-yl)methyl}benzamide
N-[(5-{[4-(3-cyclohexyl-4-hydroxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide
N-({5-[(4-{3-[(butylamino)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl)methyl}-3-nitrobenzamide
- 10 3-nitrobenzamide
N-[(5-{[4-(3-ethylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide
3-nitro-N-[(5-{[4-(5,6,7,8-tetrahydronaphthalen-1-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
4-nitro-N-[(5-{[4-(3-propylphenoxy)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide
- 15 benzamide
N-[(5-{[4-(2,4-difluorobenzoyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide
N-[(5-{[4-(2,4-difluorobenzoyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide
- 20 2-Hydroxy-N-({5-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl)methyl}benzamide
N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide
N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-2-hydroxybenzamide
- 25 hydroxybenzamide
N-{{5-({4-[4-(1,3-dithiolan-2-yl)anilino]piperidin-1-yl)sulfonyl}thien-2-yl)methyl}-3-nitrobenzamide
3-methoxy-N-[(5-{[4-(3-methoxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide
- 30 3-methoxy-N-{{5-({4-[3-(trifluoromethyl)anilino]piperidin-1-yl)sulfonyl}thien-2-yl)methyl}benzamide



- N-{{5-({4-[3-(dimethylamino)anilino]piperidin-1-yl}sulfonyl)thien-2-yl)methyl}-3-methoxybenzamide
- 3-methoxy-N-[(5-{{4-(3-propylanilino)piperidin-1-yl}sulfonyl}thien-2-yl)methyl]-benzamide
- 5 3-methoxy-N-{{5-({4-[3-(methylsulfonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl)methyl}benzamide
- 3-methoxy-N-{{5-({4-[3-(methylsulfanyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl)methyl}benzamide
- N-{{5-({4-[3-(aminosulfonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl)methyl}-3-methoxybenzamide
- 10 methyl
- N-{{5-({4-[3-(aminocarbonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl)methyl}-3-methoxybenzamide
- 3-methoxy-N-[(5-{{4-(2-methoxyanilino)piperidin-1-yl}sulfonyl}thien-2-yl)methyl]-benzamide
- 15
- N-({5-[(4-{3-nitroanilino}piperidin-1-yl)sulfonyl]thien-2-yl)methyl)-3-methoxybenzamide
- 3-methoxy-N-{{5-({4-[2-(trifluoromethyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl)methyl}benzamide
- 20 N-({5-[(4-{2-nitroanilino}piperidin-1-yl)sulfonyl]thien-2-yl)methyl)-3-methoxybenzamide
- N-{{5-({4-[4-(aminocarbonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl)methyl}-3-methoxybenzamide
- N-{{5-({4-[4-(1,3-dithiolan-2-yl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl)methyl}-3-methoxybenzamide
- 25
- N-[(5-{{4-(3-chloroanilino)piperidin-1-yl}sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide
- N-[(5-{{4-(4-chloroanilino)piperidin-1-yl}sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide
- 30 3-methoxy-N-({5-[(4-{4-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl)methyl}benzamide

- N-({5-[(4-{3-[amino(imino)methyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide
- N-({5-[(4-{3-[(2-hydroxyethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide
- 5 3-methoxy-N-({5-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide
- N-({5-[(4-anilinopiperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide
- 3-methoxy-N-({5-[(4-{3-[(trifluoromethyl)sulfanyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide
- 10 N-[(5-[(4-(4-hydroxyanilino)piperidin-1-yl)sulfonyl]thien-2-yl)methyl]-3-methoxybenzamide
- 3-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfanyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide
- 4-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfanyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide
- 15 N-[(5-[(4-(2-hydroxyanilino)piperidin-1-yl)sulfonyl]thien-2-yl)methyl]-3-methoxybenzamide
- 3-methoxy-N-[(5-[(4-(pyrimidin-2-ylamino)piperidin-1-yl)sulfonyl]thien-2-yl)methyl]benzamide
- 20 N-({5-[(4-[(3-aminopyridin-2-yl)amino]piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide
- N-[(5-[(4-[(3-nitropyridin-2-yl)amino]piperidin-1-yl)sulfonyl]thien-2-yl)methyl]-3-methoxybenzamide
- N-({5-[(4-[(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)amino]piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide
- 25 thien-2-yl)methyl]-3-methoxybenzamide
- N-[(5-[(4-(2,3-dihydro-1H-inden-5-ylamino)piperidin-1-yl)sulfonyl]thien-2-yl)methyl]-3-methoxybenzamide
- 3-methoxy-N-[(5-[(4-(2-propylanilino)piperidin-1-yl)sulfonyl]thien-2-yl)methyl]benzamide
- 30 3-methoxy-N-[(5-[(4-(4-propylanilino)piperidin-1-yl)sulfonyl]thien-2-yl)methyl]benzamide

N-[(5-{[4-(3-tert-butylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide

N-({5-[4-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]amino}piperidin-1-yl]sulfonyl}thien-2-yl)methyl)-3-methoxybenzamide

5 3-methoxy-N-({5-([4-[3-(1,3-oxazol-5-yl)anilino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl}benzamide

N-[(5-{[4-([1,1'-biphenyl]-3-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide

10 3-methoxy-N-[(5-{[4-(3-propylphenoxy)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide

3-methoxy-N-({5-([4-[3-(morpholin-4-ylsulfonyl)anilino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl}benzamide

3-methoxy-N-[(5-{[4-(2-phenylethyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide

15 N-[(5-{[4-(3-benzylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide

3-methoxy-N-[(5-{[4-(3-phenylpropyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide

20 3-methoxy-N-({5-([4-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}piperidin-1-yl]sulfonyl}thien-2-yl)methyl}benzamide

N-[(5-{[4-(3-cyclohexyl-4-hydroxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide

N-({5-[4-{[3-(butylamino)sulfonyl]anilino}piperidin-1-yl]sulfonyl}thien-2-yl)methyl)-3-methoxybenzamide

25 N-[(5-{[4-(3-ethylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide

3-methoxy-N-[(5-{[4-(5,6,7,8-tetrahydronaphthalen-1-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

30 N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-5-nitro-1H-pyrazole-3-carboxamide

N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-2-oxo-1,2-dihydropyridine-3-carboxamide

- N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-2-thioxo-1,2-dihydropyridine-3-carboxamide
- N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3,4-dihydroxybenzamide
- 5 N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-pyridine-2-carboxamide
- N-[(5-{[4-(hexyloxy)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide
- N-[(5-{[4-(heptanoyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide
- 4-chloro-N-[(5-{[4-(3-propylanilino)piperidin-1-yl]sulfonyl}-2-furyl)methyl]benzamide
- 10 4-chloro-N-[(5-{[4-(3-chloroanilino)piperidin-1-yl]sulfonyl}-2-furyl)methyl]benzamide
- 4-chloro-N-[(5-{[4-(3-methoxyanilino)piperidin-1-yl]sulfonyl}-2-furyl)methyl]benzamide
- 4-chloro-N-{[5-{[4-(3-(trifluoromethyl)anilino)piperidin-1-yl]sulfonyl}-2-furyl]methyl}benzamide
- 15 4-chloro-N-{[5-{[4-(3-(dimethylamino)anilino)piperidin-1-yl]sulfonyl}-2-furyl]methyl}benzamide
- 4-chloro-N-{[5-{[4-(3-(methylsulfonyl)anilino)piperidin-1-yl]sulfonyl}-2-furyl]methyl}benzamide
- 4-chloro-N-{[5-{[4-(3-(methylsulfonyl)anilino)piperidin-1-yl]sulfonyl}-2-furyl]methyl}benzamide
- 20 N-{[5-{[4-(3-(aminosulfonyl)anilino)piperidin-1-yl]sulfonyl}-2-furyl]methyl}-4-chlorobenzamide
- methyl 3-({1-[(5-{[(4-chlorobenzoyl)amino]methyl}-2-furyl)sulfonyl]piperidin-4-yl}amino)benzoate
- 25 3-({1-[(5-{[(4-chlorobenzoyl)amino]methyl}-2-furyl)sulfonyl]piperidin-4-yl}amino)benzamide
- 4-chloro-N-({5-[(4-{3-nitroanilino}piperidin-1-yl)sulfonyl]-2-furyl)methyl}benzamide
- 4-chloro-N-[(5-{[4-(2-methoxyanilino)piperidin-1-yl]sulfonyl}-2-furyl)methyl]benzamide
- 30 4-chloro-N-{[5-{[4-(2-(trifluoromethyl)anilino)piperidin-1-yl]sulfonyl}-2-furyl]methyl}benzamide
- 4-chloro-N-({5-[(4-{2-nitroanilino}piperidin-1-yl)sulfonyl]-2-furyl)methyl}benzamide

- 4-chloro-N-[(5-{[4-(4-chloroanilino)piperidin-1-yl]sulfonyl}-2-furyl)methyl]benzamide
- 4-chloro-N-[(5-{[4-[4-(trifluoromethyl)anilino]piperidin-1-yl]sulfonyl}-2-furyl)-methyl]benzamide
- 4-chloro-N-[(5-{[4-{4-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl]sulfonyl}-2-furyl)methyl]benzamide
- 5 N-[(5-{[4-[4-(aminocarbonyl)anilino]piperidin-1-yl]sulfonyl}-2-furyl)methyl]-4-chlorobenzamide
- 4-chloro-N-[(5-{[4-[4-(1,3-dithiolan-2-yl)anilino]piperidin-1-yl]sulfonyl}-2-furyl)-methyl]benzamide
- 10 N-[(5-{[4-{3-[amino(imino)methyl]anilino}piperidin-1-yl]sulfonyl}-2-furyl)methyl]-4-chlorobenzamide
- 4-chloro-N-[(5-{[4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl]sulfonyl}-2-furyl)methyl]benzamide
- N-[(5-{[4-anilinopiperidin-1-yl]sulfonyl}-2-furyl)methyl]-4-chlorobenzamide
- 15 4-nitro-N-[(5-{[4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl]sulfonyl}-2-furyl)methyl]benzamide
- 4-chloro-N-[(5-{[3-{3-[(trifluoromethyl)sulfonyl]anilino}pyrrolidin-1-yl]sulfonyl]thien-2-yl)methyl]benzamide
- 4-chloro-N-[(5-{[4-{3-[(trifluoromethyl)sulfonyl]anilino}azepan-1-yl]sulfonyl]thien-2-yl)methyl]benzamide
- 20

Thereby, the most preferred compounds are those which are selected from the group consisting of :

- 4-chloro-N-[(5-{[4-(2,4-difluorobenzoyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide
- 25 4-chloro-N-[(5-{[4-(phenylacetyl)-1,4-diazepan-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide
- N-[(5-{[4-anilinopiperidin-1-yl]sulfonyl]thien-2-yl)methyl]-4-chlorobenzamide
- N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide
- 30 N-[(5-{[4-(1H-benzimidazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide



- 4-chloro-N-{{5-({4-[3-propylanilino]piperidin-1-yl}sulfonyl)thien-2-yl)methyl}-benzamide
- 4-chloro-N-[(5-{{4-(4-chloroanilino)piperidin-1-yl}sulfonyl}thien-2-yl)methyl]-benzamide
- 5 4-chloro-N-({5-[(4-{3-[(2-hydroxyethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl)methyl)benzamide
- N-{{5-({4-[3-(aminosulfonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl)methyl}-4-chlorobenzamide
- 4-chloro-N-[(5-{{4-(1-naphthoyl)piperazin-1-yl}sulfonyl}thien-2-yl)methyl]benzamide
- 10 4-nitro-N-[(5-{{4-(3-methoxyanilino)piperidin-1-yl}sulfonyl}thien-2-yl)methyl]-benzamide
- methyl 3-{{1-({5-[(4-nitrobenzoyl)amino)methyl]thien-2-yl}sulfonyl)piperidin-4-yl}amino}benzoate
- N-[(5-{{4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl}sulfonyl}thien-2-yl)methyl]-2-
- 15 hydroxybenzamide
- N-({5-[(4-{2-nitroanilino}piperidin-1-yl)sulfonyl]thien-2-yl)methyl)-3-methoxybenzamide

- A further aspect of the present invention consists in the use of the sulfonamide derivatives according to formula I for the preparation of pharmaceutical compositions for the modulation – notably for the down-regulation, e.g. up to the inhibition - of the JNK function or signalling pathway associated disorders, in particular against neuronal disorders and/or against disorders of the immune system as well as said pharmaceutical compositions themselves. Preferred JNK pathways are the JNK 1 and/or 2 and/or JNK3.
- 20
- 25 As above pointed out, the compounds of formula I are suitable to be used as a medication. Some few of the compounds falling into the above generic formula I have been disclosed prior to the filing of the present application, whereby for 9 of them no medical or biological activity whatsoever was described so far. Hence, it is herein reported that both the novel and the few known compounds falling under the above set out generic
- 30 formula I are indeed suitable for use in treating disorders of the autoimmune system and neuronal system of mammals, notably of human beings. More specifically, the compounds according to formula I, alone or in the form of a pharmaceutical composition,

are useful for the modulation of the JNK pathway, more specifically for treatment or prevention of disorders associated with abnormal expression or activity of JNK, notably of JNK2 and 3. Said modulation usually preferably involves the inhibition of the JNK pathways, notably of the JNK2 and/or 3. Such an abnormal expression or activity of JNK could be triggered by numerous stimuli (e.g. stress, septic shock, oxidative stress, cytokines) and could lead to out-of-control apoptosis or autoimmune diseases that is frequently involved in the below enumerated disorders and disease states. Hence, the compounds according to formula I could be used for the treatment of disorders by modulating the JNK function or signalling pathways. Said modulation of the JNK function or pathways could involve its activation, but preferably it involves the down-regulation up to inhibition of the JNK pathways, notably of the JNK 1 and/or 2 and/or JNK3. The compounds according to formula I could be employed alone or in combination with further pharmaceutical agents, e.g. with a further JNK modulator.

Specifically, the compounds pursuant to formula I are useful for the treatment or prevention of immuno- and/or neuronal-related diseases or pathological states in which inhibition of JNK2 or JNK3 plays a critical role such as epilepsy; neurodegenerative diseases including Alzheimer's disease, Huntington's disease, Parkinson's disease; retinal diseases; spinal cord injury; head trauma, autoimmune diseases including multiple sclerosis, inflammatory bowel disease (IBD), rheumatoid arthritis; asthma; septic shock; transplant rejection; cancers including breast, colorectal, pancreatic and cardiovascular diseases including stroke, cerebral ischemia, arterosclerosis, myocardial infarction, myocardial reperfusion injury.

Quite surprisingly it turned out that the inventively found compounds according to formula I do show a considerable activity as inhibitors of JNK2 and 3. According to a preferred embodiment, the compounds according to the invention are essentially inactive in view of 2 further apoptosis modulating enzymes, i.e. p38 and/or ERK2, belonging incidentally to the same family as JNK2 and 3. Hence, the compounds according to the present invention offer the possibility to selectively modulate the JNK pathway, and in particular to treat disorders related to the JNK pathways, while being essentially inefficient with regard to other targets like said p38 and ERK2, so that they could indeed be viewed as selective inhibitors. This is of considerable significance, as these related en-

zymes are generally involved in different disorders, so that for the treatment of a distinct disorder, it is desired to employ a correspondingly selective medicament.

As a matter of fact, prior to the herein reported, surprisingly found pharmaceutically active sulfonamide derivatives according to formula I, nothing was known in respect of the use of small molecule chemical compounds as inhibitors of the JNK kinase pathway.

Still a further aspect of the present invention consists in the actually novel sulfonamide derivatives of formula I, i.e. those sulfonamide derivatives according to formula I that have not been disclosed by the prior art. Thereby, a total of 9 compounds have been disclosed by the CEREP company (www.cerep.fr) in as far as they are mentioned in a company catalogue, without any medical indication, though.

Generally, the compounds according to formula I of the CEREP company are only those wherein Ar¹ is 4-chlorophenyl and X is O and R¹ is H, Ar² is a thienyl group, while Y is a piperazino-, a 3-methyl piperazino-, a piperazino-3, 5-dione- or a piperidino group being substituted in the following way :

- where Y is a piperazino group, L¹ is diphenylmethyl, benzo[1,3]dioxol-5-yl-methyl, 4-methoxy phenyl, 2-hydroxyethyl, methyl group, 4-chlorophenyl methyl,
- where Y is a 3-methyl piperazino, L¹ is 4-chlorophenyl methyl,
- where Y is a piperazino-3, 5-dione group, L¹ is 2-phenyl ethyl, and
- where Y is a piperidino group, L¹ is H, and L² is 2-hydroxy ethyl.

Compounds according to formula I that have been disclosed by the prior art together with a medical indication are those, wherein :

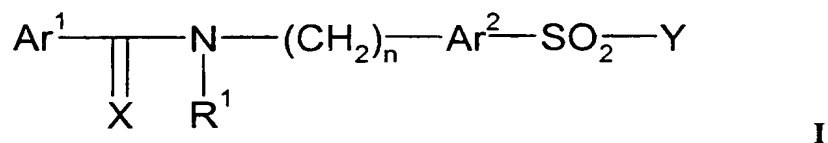
- Y is a piperidino- or a pyrrolidino group being substituted at the β -position of said sulfonamide nitrogen by one R⁶ = benzo[5, 6]cyclohepta[1, 2b]pyridine, or a benzo[5, 6]cyclohept (3,4) ene [1, 2b]pyridine, whereby Ar¹ is phenyl, Ar² is thienyl, X is oxygen, R¹ is hydrogen; L¹ and L² are H and n is 1 for the treatment of proliferative diseases (WO 96/30017).
- X is oxygen, R¹ is hydrogen and n is 1, while Y is a piperazino group, whereby L¹ is a substituent that includes a phenyl being imperatively substituted by a



group $-C(=NH)-NH_2$ (benzamidine) or a protected form thereof to be used as factor XA inhibitors (WO 99/16751).

- Two further compounds are rather incidentally disclosed in WO 97/45403 (i.e. 2-{[2-(benzoylaminomethyl)-thiophene]-5-sulfonyl}-1,2,3,5,6,7-hexahydro-N,N-dipropylcyanopent[f]isoindol-6-amine as selective dopamine D3 ligand) and in WO 97/30992 (i.e. N-[[5-[[7-cyano-1,2,3,5-tetrahydro-1-(1H-imidazol-4-yl-methyl)-3-(phenylmethyl)-4H-1,4-benzodiazepin-4-yl]sulfonyl]-2-thienyl]methyl] benzamide and its hydrochloride to be used for inhibiting farnesyl-protein transferase).
- Finally, compounds of formula I wherein X is oxygen and Y is a 4-8 membered saturated cyclic alkyl containing one or two nitrogen atoms, said Y being imperatively substituted by an amido group $(C=O)N(R,R')$ at the alpha position of the sulfonamide nitrogen are disclosed within WO 98/ 53814. Said compounds are mentioned to be useful in the inhibition of cell adhesion.

- Hence, the entirely novel sulfonamide derivatives are those of the below set out general formula I whereby the above identified known compounds are excluded.

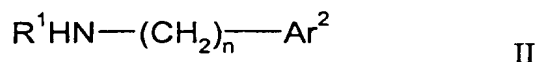


Still a further object of the present invention is a process for preparing the novel sulfamide derivatives according to formula I which have been set out above.

- The sulfonamide derivatives of this invention can be prepared from readily available starting materials using the following general methods and procedures.

It will be appreciated that where typical or preferred experimental conditions (i.e., reaction temperatures, time, moles of reagents, solvents, etc.) are given, other experimental conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimisation procedures.

In a preferred method of synthesis, the sulfonamide derivatives of the invention are prepared by first coupling an amine of formula II:

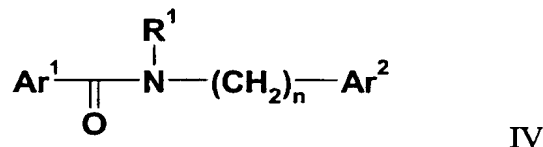




where Ar² and R¹ are as defined above, with an acyl chloride of formula III:



where Ar¹ is as defined above, to provide an amide of formula IV:



5 Amines of formula II are either known compounds or can be prepared from known compounds by conventional procedures. Preferred amines as starting materials include thien-2-yl-methylamine, furan-2-yl-methylamine, pyridyl-2-ylmethylamine and the like. The acyl chlorides of formula III are also commercially available or previously described compounds. Preferred acyl chlorides include 4-chlorobenzoyl chloride, 4-fluoroben-
10 zoyl chloride, 4-trifluoromethylbenzoyl chloride and the like. If not known, the acid halide can be prepared by reacting the corresponding carboxylic acid with an inorganic acid halide, such as thionyl chloride, phosphorus trichloride or oxalyl chloride under conventional conditions.

Generally, this reaction is performed upon using about 1 to 5 molar equivalents of the
15 inorganic acid halide or oxalyl chloride, either in pure form or in an inert solvent, such as carbon tetrachloride, at temperature in the range of about 0°C to about 80°C for about 1 to about 48 hours. A catalyst, as *N,N*-dimethylformamide, may also be used in this reaction.

When an acyl halide is employed in the coupling reaction, it is typically reacted with
20 amine II in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of example, triethylamine, diisopropylethylamine, *N*-methylmorpholine and the like. Alternatively, an excess of amine II may be used to scavenge the acid generated during the reaction.

Alternatively, the carboxylic acid of compound III can be employed in the coupling re-
25 action. The carboxylic acid of III are usually commercially available reagents or can be prepared by conventional procedures.

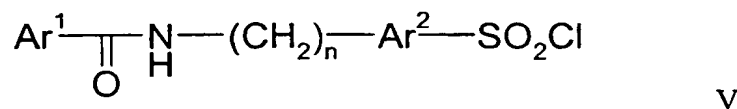
The coupling reaction of carboxylic acid of III (i.e. the acyl chloride) is conducted upon using any conventional coupling reagent including, for example, carbodiimides such as



dicyclohexylcarbodiimide, N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide and other promoting agents, such as *N,N*-carbonyl-diimidazole or PyBOP. This reaction can be conducted with or without the use of well known additives such as *N*-hydroxysuccinimide, 1-hydroxybenzotriazole, etc. which are known to facilitate the coupling of carboxylic acids and amines.

The coupling reaction using either acid halide III or its carboxylic acid is preferably conducted at a temperature of from about 0°C to about 6°C for about 1 to about 24 hours. Typically, the reaction is conducted in an inert aprotic polar solvent such as *N,N*-dimethylformamide, dichloromethane, chloroform, acetonitrile, tetrahydrofuran and the like using about 1 to about 5 molar equivalents of the amine based on the carboxylic acid or its acid halide. Upon completion of the reaction, the carboxamide IV is recovered by conventional methods including precipitation, chromatography, filtration, distillation and the like.

The sulfonyl chlorides of formula V necessary for the preparation of the sulfonylpiperidines or piperazines of formula I are prepared using conventional sulfonylation methods:



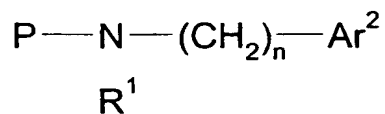
A preferred sulfonylation reagent for use in this reaction is chlorosulfonic acid. Typically, the sulfonylation reaction is performed by treating the carboxamide of formula (IV) with about 5 to about 10 molar equivalent of the sulfonylation reagent in an inert solvent, such as dichloromethane, at a temperature ranging from about -70°C to about 50°C. Preferably, the addition of chlorosulfonic acid takes place at -70°C and leads to the formation of the intermediate sulfonic acid. Increasing the temperature to 20°C allows the formation of the sulfonyl chloride of formula V.

According to a further preferred method of preparation notably in case that the above pointed out method leading to the preliminary synthesis of sulfonyl chloride of formula V is not applicable, the sulfonyl piperidines and piperazines of this invention are prepared by the following steps:

- Protection of the amine function of compounds of formula II;
- Chlorosulfonylation of the aromatic group;
- Formation of the sulfonamide function;

- Deprotection of the protectiong group;
- Acylation of the above generated free amine;

Amines of formula II are protected with a suitable protecting group of an amine moiety to provide intermediate of formula VI wherein P denotes the protecting group.

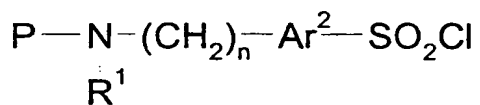


VI

Numerous protecting groups P of the amine function as well as their introduction and removal, are well described in T.W. Greene and G.M. Wuts, *Protecting groups in Organic Synthesis*, Third Edition, Wiley, New York, 1998, and references cited therein. Preferred are protecting groups that are acids and bases stable and can be further re-
 10 moved by using metal transition complexes such as palladium complexes, for example the allylcarbamate group (Alloc) or the N,N'-bisallyl group. Another preferred protecting group is the maleimide group which is stable in a all range of experimental conditions.

The introduction of said groups can be performed by reacting the corresponding bisal-
 15 lylcarbonate anhydride or allylbromide or maleic anhydride in the presence of a base such as triethylamine, diisopropylethylamine, *N*-methylmorpholine and the like in an aprotic solvent such as N,N-dimethylformamide, dichloromethane, chloroform, acetonitrile, tetrahydrofuran and the like at a temperature ranging from about 0°C to about 80°C.

20 Compounds of formula VI are then sulfonated using a conventional very mild sulfonating procedure that allows the obtention of sulfonyl chloride of formula VII.



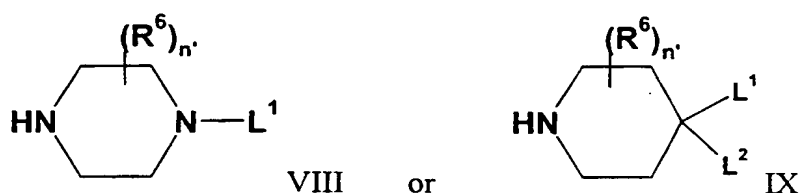
VII

Typically, protected amine VI is treated with a base such as n-butyllithium or tert-butyl-
 25 lithium under an inert atmosphere, in a polar aprotic solvent such as tetrahydrofuran, ether or dioxane at a temperature ranging from -70°C to 0°C during a time ranging from 15 minutes to 4 hours. The so formed anion is then treated with SO₂Cl₂ or most preferably SO₂ by bubbling the gas into the reaction mixture at a temperature ranging from -70°C to 20°C during a time ranging from 5 minutes to 1 hour. The sulfonate obtained is

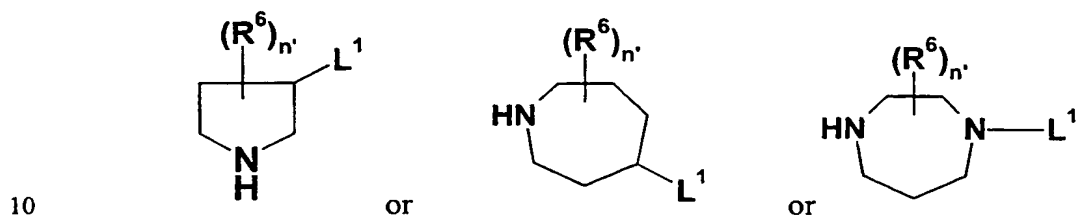


°C to 20°C during a time ranging from 5 minutes to 1 hour. The sulfonate obtained is then transformed "*in situ*" to the sulfonyl chloride of formula VII by contacting with *N*-chlorosuccinimide at a temperature ranging from 0°C to 70°C.

The sulfonamide derivatives of formula I are then prepared from the corresponding
 5 above mentioned sulfonyl chloride V or VII, by reaction with a corresponding cyclic amine, e.g. either with a piperazine or piperidine derivative of the general formula VIII or IX.



or a pyrrolidine, an azepan or a 1,4-diazepan of the below formulas



whereby R^6 , n , L^1 and L^2 are as above defined.

The above set out cyclic amines, notably those of formula VIII or IX are either commercially available compounds or compounds that can be prepared by known procedures.

15 Typically, piperazines of type VIII can be prepared upon using conventional methods known by a person skilled in the art.

For L^1 and/or L^2 = aryl, suitable methods of preparation are described in *Tetrahedron Lett.* **1996**, 37, 8487-8488 and references cited therein.

For L^1 and/or L^2 = aryl C_1 - C_6 alkyl, a further preferred method is the reaction of the cor-
 20 responding piperazine or mono-*N*-protected piperazine with compounds of formula X

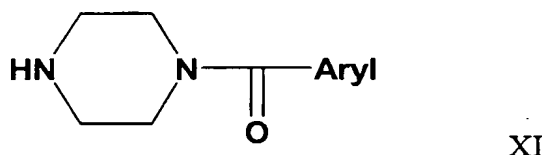


wherein X is Cl, Br, I, OTs, OMs



The reaction is generally conducted in the presence of a base such as triethylamine, diisopropylethylamine, potassium carbonate and the like in solvent such as N,N-dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone, ethanol, acetonitrile at a temperature from about 0° to about 100°C.

- 5 For L^1 and/or $L^2 = -C(S)-$, a further preferred method is the conversion of compounds of type XI using the Lawesson's reagent which allows the transformation of an amide into a thioamide group as described in *Bull. Soc. Chim. Belgium*, **1978**, 87, 229.



- The sulfonamides of formula I are readily prepared by contacting the sulfonyl chlorides
10 V with an amine of formula VIII in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of examples, triethylamine, diisopropylethylamine, N-methylmorpholine and the like. The reaction is preferably conducted in solvent such as N,N-dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone, ethanol, acetonitrile at a temperature from about 0° to about 100°C.
- 15 Alternatively, the sulfonamide derivatives of formula I are readily prepared from the corresponding sulfonyl chloride V or VII, by reaction with a piperidine of general formula IX. Piperidines of formula IX are either commercially available compounds or compounds that can be prepared by known procedures. Typically, piperidines of type IX can be prepared using conventional methods known by one skilled in the art and described by way of examples in *J. Pharm. Sci.* **1972**, 61, 1316; *J. Heterocyclic. Chem.*, **1986**, 23, 73; *Tetrahedron Lett.*, **1996**, 37, 1297, US 5106983, WO/9113872 and
20 WO/9606609.

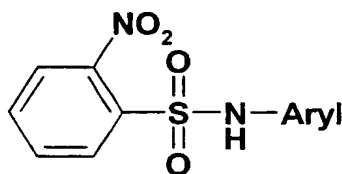
Preferred methods of obtaining piperidines of formula IX are the following:

- For $L^1 = H$ and $L^2 = (CH_2)_n\text{-Aryl}$ wherein $n = 0, 1, 2$; addition of an organometallic species such as $Ar^3(CH_2)_nLi$ or $Ar^3(CH_2)_nMgBr$ on mono-protected 4-piperidone followed
25 by reduction of the so-formed double bond which allows the formation of compounds of type IX.



For $L^2 = -NR-(CH_2)_n\text{-Aryl}$ wherein $n = 0, 1, 2$, a preferred method is the reductive amination of 4-piperidone with amines of type $\text{Aryl}-(CH_2)_n\text{-NR-H}$.

A further preferred method in the case where $n = 0$ is a "Mitsunobu type" coupling between an activated aniline of type XII with mono-N-protected 4-piperidol as described
 5 in *Tetrahedron Lett.* **1995**, 36, 6373-6374.

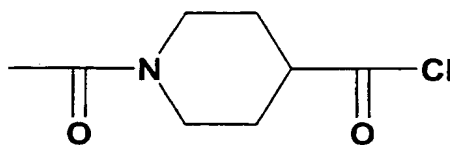


XII

Deprotection of the sulfamino group is then carried out using thiophenol in the presence of potassium carbonate.

For $L^2 = -NR^3\text{'C(O)R}^3$, $-NR^3\text{'C(O)NR}^3\text{'R}^3$, $NR^3\text{'SO}_2\text{-R}^3$, a preferred method of synthesis of compounds of formula IX is the reaction of commercially available N-BOC-4-aminopiperidine with respectively acyl chlorides, isocyanates and sulfonyl chloride under classical conditions very well known by one skilled in the art.
 10

When $L^2 = -CO\text{-Aryl}$, compounds of formula IX are readily prepared by contacting well chosen aromatic or heteroaromatic rings with intermediate of type XIII



XIII

15

in the presence of a Lewis acid such as aluminum trichloride or titanium tetrachloride in a polar aprotic solvent such as dichloromethane. Intermediate XIII can be easily obtained by first acetylation of piperid-4-yl carboxylic acid and their formation of the acyl chloride by treatment with thionyl chloride.

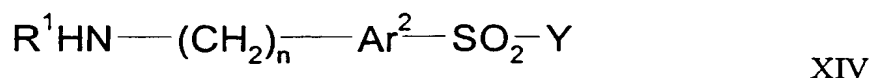
20

The sulfonamides of formula I are readily prepared by contacting the sulfonyl chloride V with an amine of formula IX in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of examples, triethylamine, diisopropylethylamine, N-methylmorpholine and the like. The reaction is prefera-

bly conducted in solvent such as N,N-dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone, ethanol, acetonitrile at a temperature from about 0° to about 100°C.

The sulfonamides of formula XIV are readily prepared by contacting the sulfonyl chloride VII with an amine of formula VIII or IX in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of examples, triethylamine, diisopropylethylamine, N-methylmorpholine and the like. The reaction is preferably conducted in solvent such as N,N-dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone, ethanol, acetonitrile at a temperature from about 0° to about 100°C.

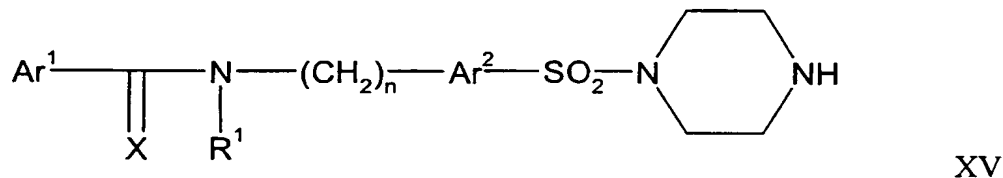
The use of sulfonyl chloride of type VII leads to amines that have to be deprotected using well known methods by one skilled in the art to afford amine of general formula XIV



wherein R^1 , Ar^2 , Y and n are as above defined.

Derivatives of type XIV are then acylated according to described methods for the preparation of amides by condensation of amines with acid chlorides or carboxylic acids in the preferred conditions described above leading to compounds of general formula I

In the particular case of compounds of general formula I where Y represents a piperazine derivative, an alternative method of preparation which has also to be considered as part of this invention, said method of preparation consisting in the condensation of a piperazine derivative of formula XV



with electrophiles L^1 which will be chosen depending on the nature of L^1 (see the above definition of L^1 , L^2). Procedures and methods to perform these types of condensation are well-known and have been well described on various synthesis of N-substituted piperazine derivatives.

If the above set out general synthetic methods are not applicable for obtaining compounds of formula I, suitable methods of preparation known by a person skilled in the art should be used. For example, when Ar² is phenyl, one should start from commercially available 4-cyanophenyl sulfonyl chloride and applies conventional methods
5 known by a person skilled in the art to reach sulfonamide derivatives of formula I. A final aspect of the present invention is related to the use of the compounds according to formula I for the modulation of the JNK function, or signaling pathways, the use of said compounds for the preparation of pharmaceutical compositions for the modulation of the JNK pathway as well as the formulations containing the active compounds ac-
10 cording to formula I. Said modulation of the JNK pathway is viewed as a suitable approach of treatment for various disorders. When employed as pharmaceuticals, the sulfonamide derivatives of the present invention are typically administered in the form of a pharmaceutical composition. Hence, pharmaceutical compositions comprising a compound of formula I and a pharmaceutically acceptable carrier, diluent or excipient there-
15 fore are also within the scope of the present invention. A person skilled in the art is aware of a whole variety of such carrier, diluent or excipient compounds suitable to formulate a pharmaceutical composition. Also, the present invention provides compounds for use as a medicament. In particular, the invention provides the compounds of formula I for use as JNK inhibitor, notably JNK2 and JNK3, for the treatment of disor-
20 ders of the immune as well as the neuronal system of mammals, notably of humans, either alone or in combination with other medicaments.

The compounds of the invention, together with a conventionally employed adjuvant, carrier, diluent or excipient may be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or
25 filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, or in the form of sterile injectable solutions for parenteral (including subcutaneous use). Such pharmaceutical compositions and unit dosage forms thereof may comprise ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain
30 any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

When employed as pharmaceuticals, the sulfonamides derivatives of this invention are typically administered in the form of a pharmaceutical composition. Such compositions can be prepared in a manner well known in the pharmaceutical art and comprise at least one active compound. Generally, the compounds of this invention are administered in a pharmaceutically effective amount. The amount of the compound actually administered will typically be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

- 10 The pharmaceutical compositions of these inventions can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. Depending on the intended route of delivery, the compounds are preferably formulated as either injectable or oral compositions. The compositions for oral administration can take the form of bulk liquid solutions or suspensions, or bulk powders.
- 15 More commonly, however, the compositions are presented in unit dosage forms to facilitate accurate dosing. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Typical unit dosage
- 20 forms include prefilled, premeasured ampoules or syringes of the liquid compositions or pills, tablets, capsules or the like in the case of solid compositions. In such compositions, the sulfonamide compound is usually a minor component (from about 0.1 to about 50% by weight or preferably from about 1 to about 40% by weight) with the remainder being various vehicles or carriers and processing aids helpful for forming the desired
- 25 dosing form.

Liquid forms suitable for oral administration may include a suitable aqueous or non-aqueous vehicle with buffers, suspending and dispensing agents, colorants, flavors and the like. Solid forms may include, for example, any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatine; an excipient such as starch or lactose, a disintegrating agent such as

30 alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate; a glidant

such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

Injectable compositions are typically based upon injectable sterile saline or phosphate-buffered saline or other injectable carriers known in the art. As above mentioned, the
5 sulfonamide compound of formula I in such compositions is typically a minor component, frequently ranging between 0.05 to 10% by weight with the remainder being the injectable carrier and the like.

The above described components for orally administered or injectable compositions are merely representative. Further materials as well as processing techniques and the like
10 are set out in Part 8 of *Remington's Pharmaceutical Sciences*, 17th Edition, 1985, Marck Publishing Company, Easton, Pennsylvania, which is incorporated herein by reference. The compounds of this invention can also be administered in sustained release forms or from sustained release drug delivery systems. A description of representative sustained release materials can also be found in the incorporated materials in *Remington's Pharmaceutical Sciences*.
15

In the following the present invention shall be illustrated by means of some examples which are not construed to be viewed as limiting the scope of the invention.

Examples

Protocol #1

20 **Example 1: Preparation of 4-chloro-N-[5-(piperazine-1-sulfonyl)-thiophen-2-yl-methyl]-benzamide 1**

4-Chloro-N-thiophen-2-ylmethyl-benzamide 1a

A solution of 4-chlorobenzoyl chloride (0.114 mol) in 50 mL dry CH₂Cl₂ was added
25 over 30 min to a stirred solution of 2-aminomethyl-thiophene (0.137 mol) and ¹Pr₂NEt (0.25 mol) in CH₂Cl₂ (200 mL) at 0°C. A white solid was formed and the reaction was allowed to warm to room temperature over 1 h. The mixture was diluted with 200 mL of CH₂Cl₂, washed twice with HCl aq. (0.1N) and dried over MgSO₄. Evaporation of the solvents afforded 28 g (98%) of the title benzamide as a white solid: m.p. 153-54°C, ¹H
30 NMR (CDCl₃) δ 7.9 (d, J = 8.67 Hz, 2H), 7.58 (d, J = 8.67 Hz, 2H), 7.44 (dd, J = 3.77,

1.13 Hz, 1H), 7.22 (d, $J = 5.27$ Hz, 1H), 7.16 (dd, $J = 3.39, 5.27$ Hz, 1H), 6.62 (br d, 1H), 4.98 (d, $J = 5.65$ Hz, 2H).

5-({[1-(4-Chloro-phenyl)-methanoyl]-amino}-methyl)-thiophene-2-sulfonyl chloride **1b**

Chlorosulfonic acid (20.1 mL, 198 mmol) in CH_2Cl_2 (80 mL) was added dropwise to a solution of **1a** (10 g, 40 mmol) in CH_2Cl_2 (500 mL) at -80°C . The mixture was allowed to reach room temperature in 5h.. The reaction mixture was poured on ice and quickly extracted with CH_2Cl_2 . The organic layer was dried over MgSO_4 and the solvent was evaporated to dryness which afforded 8.8 g (63%) of desired sulfonyl chloride **1b**; mp $133-35^\circ\text{C}$, ^1H NMR ($\text{DMSO}-d_6$) δ 9.21 (t, $J = 6.4$ Hz, 1H), 7.87 (d, $J = 8.67$ Hz, 2H), 7.53 (d, $J = 8.67$ Hz, 2H), 6.91 (d, $J = 3.39$ Hz, 1H), 6.77 (d, $J = 3.39$ Hz, 1H), 4.53 (d, $J = 3.77$ Hz, 2H).

4-Chloro-N-[5-(piperazine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide **1**

A solution of **1b** (1 g, 2.9 mmol) in 0.5 mL DMF and 2 mL CH_2Cl_2 was added slowly at 0°C to piperazine (985 mg, 11.4 mmol) in CH_2Cl_2 (11 mL). The reaction was stirred for 2h while room temperature was reached. The reaction mixture was washed with sat. NaHCO_3 and dried over MgSO_4 . After evaporating the solvent 1.76 g (62%) of **1c** was isolated. ^1H NMR ($\text{DMSO}-d_6$) δ 9.38 (t, $J = 5.27$ Hz, 1H), 7.90 (d, $J = 8.67$ Hz, 2H), 7.56 (d, $J = 8.67$ Hz, 2H), 7.46 (d, $J = 3.77$ Hz, 1H), 7.18 (d, $J = 4.14$ Hz, 1H), 4.67 (d, $J = 6.03$ Hz, 2H), 2.66-2.84 (m, 8H).

Example 2 : Preparation of 4-Chloro-N-{5-[4-(3-Trifluoromethanesulfonyl)-phenylamino]-piperidine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **2**

To a stirred solution of 4-((3-Trifluoromethanesulfonyl)-phenylamino)-piperidine (580 mg, 1.88 mmol) and $i\text{Pr}_2\text{NEt}$ (1.46 μL , 8.6 mmol) in CH_2Cl_2 (250 mL) was added **1b** (600 mg, 1.71 mmol) in DMF/ CH_2Cl_2 (1:3, 15 mL). After 3 h the reaction mixture was washed with HCl (0.1 N) and sat. NaCl solution, and dried over MgSO_4 . The solvent was evaporated and the residue was filtered through silica gel using cyclohexane/ethylacetate 1:1 as eluent. **2** was isolated as white solid (840 mg, 79%). mp.: $198-199^\circ\text{C}$. ^1H NMR ($\text{DMSO}-d_6$) δ 9.38 (t, $J = 5.6$ Hz, 1H), 7.74 (d, $J = 8.6$ Hz, 2H), 7.45-7.33 (m, 4H), 7.28 (d, $J = 7.9$ Hz, 1H), 7.06 (d, $J = 3.8$ Hz, 1H), 7.02 (s, 1H), 6.90 (d, $J = 7.9$ Hz, 1H), 6.69 (t, $J = 5.6$ Hz, 1H), 4.68 (d, $J = 5.6$ Hz, 2H), 4.00 (s, b, Hz, 1H), 3.71 (d, $J = 12.1$ Hz, 2H), 3.32 (s, b, 1H), 2.62 (dd, $J = 12.1$ Hz, 2.26 Hz, 2H), 2.11 (d,

$J = 13.56$ Hz, 2H), 1.65-1.48 (m, 2H). M/Z APCI: 622.2 (M+1), 620.1 (M-1).

$C_{24}H_{23}ClF_3N_3O_5S_3$ Calc.: C: 46.34%. H: 3.73%. N: 6.75%. Found: C: 46.05%, H: 3.84%, N: 6.69%.

- 5 Alternatively 2 can be synthesised in a parallel solution phase approach.

In a 4 mL Alltech[®] tube 1 eq. of amine is shaken with polymerbound NMM (4eq.) in 1.2 mL CH_2Cl_2 /DMF. After 15 min 1 mL of a stock solution of 1b in CH_2Cl_2 /DMF (1.2eq.) is added and the reaction slurry is shaken. After 3h Aminomethyl Merryfield resin (0.4 eq) is added and the reaction is shaken overnight. The solution is filtered off,
10 the resins are washed 3 x with CH_2Cl_2 , and the solvents are evaporated at medium temperature in a Savant Speed Vac[®] Plus vacuum centrifuge for 1h.

The following compounds were prepared on a parallel fashion according to the examples described above

The following table provides HPLC data and mass spectroscopy data of the mentioned
15 examples. ^{1,2}.

Exemple	Name	Rt HPLC	Purity	Gradient HPLC	Mass M+1	Mass M
3	4-chloro-N-({5-[(4-pyridin-2-yl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl)benzamide	17.87	97	c	477	475
4	4-chloro-N-[(5-({4-(4-fluorobenzoyl)piperidin-1-yl)sulfonyl}thien-2-yl)methyl)benzamide	15.33	96.2	b		
5	4-chloro-N-({5-({4-(4-(trifluoromethyl)phenyl)piperazin-1-yl}sulfonyl)thien-2-yl)methyl}-benzamide	15.82	93	b	545	543
6	4-chloro-N-({5-[(4-{2-nitrophenyl}piperazin-1-yl)sulfonyl]thien-2-yl)methyl)benzamide	14.43	99	b	521	519
7	4-chloro-N-({5-[(4-{4-nitrophenyl}piperazin-1-yl)sulfonyl]thien-2-yl)methyl)benzamide	13.99	93.3	b	522	520
8	4-chloro-N-[(5-({4-(2-furoyl)piperazin-1-yl)sulfonyl}thien-2-yl)methyl)benzamide	11.76	82	b	494	492
9	4-chloro-N-[(5-({4-(4-hydroxyphenyl)piperazin-1-yl)sulfonyl}thien-2-yl)methyl)benzamide	11.98	78	b	492	490
10	4-chloro-N-[(5-({4-(2-oxo-2-pyrrolidin-1-ylethyl)piperazin-1-yl)sulfonyl}thien-2-yl)methyl)benzamide	11.05	90	b	511	509
11	4-chloro-N-[(5-({4-(2-morpholin-4-yl-2-oxoethyl)piperazin-1-yl)sulfonyl}thien-2-yl)methyl]-benzamide	10.44	89	b	527	525

¹ HPLC conditions: C8 Symmetry a- MeCN, 0.09%TFA, 0 to 100% (10min)

HPLC conditions: C18 b- MeCN, 0.09%TFA, 0 to 100% (20min), c- MeCN, 0.09%TFA, 0 to 100% (30min).

² Mass spectrum APCI

12	4-chloro-N-[(5-{[4-(pyridin-4-ylmethyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	11.62	89	b	491	489
13	4-chloro-N-[(5-{[4-(2-thien-2-ylethyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	14.58	90	b	510	508
14	4-chloro-N-[(5-{[4-(3,5-dimethoxyphenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	14.04	93	b	536	534
15	4-chloro-N-[(5-{[4-(cyclohexylmethyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	17.27	88	b	496	494
16	4-chloro-N-[(5-{[4-(2-methoxyphenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	14.59	88	b	506	504
17	N-(5-{[4-(4-benzylpiperazin-1-yl)sulfonyl]thien-2-yl}methyl)-4-chlorobenzamide	14.75	82	b	490	488
18	4-chloro-N-[(5-{[4-(2-phenylethyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	10.27	93	b	504	502
19	4-chloro-N-[(5-{[4-(4-fluorobenzyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	14.82	91	b	508	506
20	4-chloro-N-[(5-{[4-(2-cyanophenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	14.14	87	b	501	499
21	4-chloro-N-[(5-{[4-(4-chloro-3-(trifluoromethyl)-phenyl]piperazin-1-yl}sulfonyl)thien-2-yl)methyl]-benzamide	16.49	94	b	578.5	576.5
22	4-chloro-N-[(5-{[4-(3-piperidin-1-ylpropyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide	7.87	95	b	525	523
23	4-chloro-N-[(5-{[4-(4-chloro-2-nitrophenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	15.38	99	b	555.5	553.4
24	4-chloro-N-[(5-{[4-(6-methylpyridin-2-yl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	9.3	91	b	491	489
25	4-chloro-N-[(5-{[4-(4-hydroxy-4-phenylpiperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide	12.84	94	b	491	489
26	N-(5-{[4-(4-benzoylpiperidin-1-yl)sulfonyl]thien-2-yl}methyl)-4-chlorobenzamide	14.35	90	b	503	501
27	4-chloro-N-[(5-{[4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	12.22	93	b	531	529
28	N-(5-{[4-(4-benzylpiperidin-1-yl)sulfonyl]thien-2-yl}methyl)-4-chlorobenzamide	16.03	93	b	489	487
29	4-chloro-N-[(5-{[4-(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-8-yl)sulfonyl]thien-2-yl}methyl)benzamide	13.14	89	b	545	543
30	4-chloro-N-[(5-{[4-(2-(methylanilino)-2-oxoethyl]piperazin-1-yl}sulfonyl)thien-2-yl)methyl]-benzamide	9.86	97	b	547	545
31	4-chloro-N-[(5-{[4-(4-hydroxy(diphenyl)methyl]piperidin-1-yl}sulfonyl)thien-2-yl)methyl]-benzamide	15.36	96	b	581	579
32	4-chloro-N-[(5-{[4-(3-cyanopyrazin-2-yl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	13.06	86	b	503	501
33	4-chloro-N-[(5-{[4-(5-nitropyridin-2-yl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	13.76	76	b	522	520
34	4-chloro-N-[(5-{[4-(3-chloro-5-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}sulfonyl)thien-2-yl)methyl]benzamide	16.32	90	b	579.5	577.6
35	4-chloro-N-[(5-{[4-(5-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}sulfonyl)thien-2-yl)methyl]-benzamide	14.88	80	b	545	543
36	4-chloro-N-[(5-{[4-(3-(trifluoromethyl)pyridin-2-	14.63	95	b	545	543

	yl]piperazin-1-yl)sulfonyl]thien-2-yl)methyl}-benzamide					
37	4-chloro-N-[(5-{[4-(2,4-difluorobenzoyl)piperidin-1-yl)sulfonyl]thien-2-yl)methyl]benzamide	14.72	95	b	539	537
38	methyl 5-{4-[(5-{[(4-chlorobenzoyl)amino]-methyl}thien-2-yl)sulfonyl]piperazin-1-yl}-7-(trifluoromethyl)thieno[3,2-b]pyridine-3-carboxylate	16.13	93	b	659	657
39	ethyl 2-{4-[(5-{[(4-chlorobenzoyl)amino]methyl}-thien-2-yl)sulfonyl]piperazin-1-yl}-5-cyano-6-methylnicotinate	14.97	89	b	588	586
40	4-chloro-N-{[5-{[4-[5-cyano-4,6-bis(dimethyl-amino)pyridin-2-yl]piperazin-1-yl)sulfonyl]thien-2-yl)methyl}benzamide	12.79	85	b	588	586
41	4-chloro-N-{[5-{[4-[6-methyl-2-(trifluoromethyl)-quinolin-4-yl]piperazin-1-yl)sulfonyl]thien-2-yl)methyl}benzamide	15.88	96	b	609	607
42	tert-butyl 4-[(5-{[(4-chlorobenzoyl)amino]-methyl}thien-2-yl)sulfonyl]piperazine-1-carboxylate	14.04	94	b	500	498
43	2-{4-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperazin-1-yl}-8-ethyl-5-oxo-5,8-dihydropyrido[2,3-d]pyrimidine-6-carboxylic acid	12.9	73	b	617	615
44	7-{4-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperazin-1-yl}-1-ethyl-6-fluoro-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylic acid	13.05	87	b	634	632
45	7-{4-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperazin-1-yl}-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid	13.1	96	b	633	631
46	4-chloro-N-[(5-{[4-(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]piperazin-1-yl)sulfonyl]thien-2-yl)methyl]benzamide	13.5	95	b	562	560
47	4-chloro-N-{[5-{[4-[(2E)-3-phenylprop-2-enyl]piperazin-1-yl)sulfonyl]thien-2-yl)methyl}-benzamide	10.65	93	b	516	514
48	4-chloro-N-[(5-{[4-(3-phenylpropyl)piperazin-1-yl)sulfonyl]thien-2-yl)methyl]benzamide	10.61	97	b	518	516
49	4-chloro-N-[(5-{[4-(3,4,5-trimethoxyphenyl)piperazin-1-yl)sulfonyl]thien-2-yl)methyl]-benzamide	13.16	90	b	566	564
50	N-[(5-{[4-(4-tert-butylbenzyl)piperazin-1-yl)sulfonyl]thien-2-yl)methyl]-4-chlorobenzamide	11.81	95	b	546	544
51	4-chloro-N-[(5-{[4-(4-fluorophenyl)piperazin-1-yl)sulfonyl]thien-2-yl)methyl]benzamide	14.93	90	b	494	492
52	4-chloro-N-[(5-{[4-(2-hydroxyphenyl)piperazin-1-yl)sulfonyl]thien-2-yl)methyl]benzamide	12.1	93	b	492	490
53	4-chloro-N-{[5-{[4-[4-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl)sulfonyl]thien-2-yl)methyl}benzamide	14.42	91	b	545	543
54	4-chloro-N-[(5-{[4-(5-cyanopyridin-2-yl)piperazin-1-yl)sulfonyl]thien-2-yl)methyl]benzamide	13.15	94	b	502	500
55	tert-butyl 1-[(5-{[(4-chlorobenzoyl)amino]-methyl}thien-2-yl)sulfonyl]piperidin-4-ylcarbamate	13.77	98	b	514	512
56	4-chloro-N-{[5-{[4-(phenylpiperazin-1-yl)sulfonyl]thien-2-yl)methyl}benzamide	14.18	94	b	476	474
57	4-chloro-N-{[5-(piperidin-1-ylsulfonyl)thien-2-yl)methyl}benzamide	13.13	96	b	399	397
58	4-chloro-N-[(5-{[4-(1-naphthyl)piperazin-1-yl)sulfonyl]thien-2-yl)methyl]benzamide	16.38	75	b	526	524



59	4-chloro-N-[(5-{[4-(3,4-dichlorophenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	16.48	81	b	545	543
60	4-chloro-N-[(5-{[4-[3-(trifluoromethyl)phenyl]piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide	15.86	93	b	544	542
61	4-chloro-N-[(5-{[3-hydroxy-4-[3-(trifluoromethyl)phenyl]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide	14.79	95	b	559	557
62	4-chloro-N-[(5-{[4-(2-methylphenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	15.64	79	b	490	488
63	N-[(5-{[(1R,4R)-5-benzyl-2,5-diazabicyclo[2.2.1]hept-2-yl]sulfonyl}thien-2-yl)methyl]-4-chloro-benzamide	9.51	97	b	502	500
64	N-[(5-{[4-(benzyloxy)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide	15.08	93	b	505	503
65	4-chloro-N-[(5-{[4-(2-chlorodibenzo[b,f][1,4]-oxazepin-1-yl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	12.86	94	b	627.5	625.6
66	N-(4-chlorophenyl)-2-(5-{[4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)acetamide	12.76	84	b	531	529
67	4-chloro-N-[(5-{[4-(4-hydroxypiperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide	10.35	95	b	415	413
68	N-[(5-{[4-(4-acetylphenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide	13.15	96	b	518	516
69	4-chloro-N-[(5-{[4-(3,5-dichloropyridin-4-yl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide	13.89	92	b	546	544
70	4-chloro-N-[(5-{[4-(3-methoxyphenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	14.24	89	b	506	504
71	N-[(5-{[4-(4-benzyl-4-hydroxypiperidin-1-yl)sulfonyl]thien-2-yl}methyl)-4-chlorobenzamide	13.72	92	b	505	503
72	N-[(5-{[4-[(2-tert-butyl-1H-indol-5-yl)amino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide	11.55	97	b	585	583
73	4-chloro-N-[(5-{[4-[(phenylacetyl)amino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	12.61	88	b	532	530
74	4-chloro-N-[(5-{[4-(tetrahydrofuran-2-ylcarbonyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide	10.87	94	b	498	496
75	4-chloro-N-[(5-{[4-(6-chloropyridin-2-yl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	14.93	95	b	511	509
76	4-chloro-N-[(5-{[4-(4-chlorophenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	15.49	91	b	510	508
77	N-[(5-{[4-(2H-1,2,3-benzotriazol-2-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide	6.57	89	a	516	514
78	4-chloro-N-[(5-{[4-(4-chlorobenzoyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	6.99	92.1	b	537	535
79	4-chloro-N-[(5-{[4-(phenoxypiperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide	6.81	72	a	491	489
80	N-[(5-{[4-(benzyl(methyl)amino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide	4.93	93.3	a	518	516
81	4-chloro-N-[(5-{[4-[3-(2,4-dichlorophenyl)-1H-pyrazol-5-yl]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	6.89	92.6	a	609	607
82	4-chloro-N-[(5-{[4-(5-thien-2-yl-1H-pyrazol-3-yl)piperidin-1-yl]sulfonyl}thien-2-	5.93	93.8	a	547	545

	yl)methyl]benzamide					
83	4-chloro-N-[(5-{[4-(2,3,4,5,6-pentamethylbenzoyl)-piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide	7.48	90.6	a	573	571
84	4-chloro-N-[(5-{[4-(phenylacetyl)-1,4-diazepan-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	5.83	94.5	a	532	530
85	4-chloro-N-[(5-{[4-[5-(4-methoxyphenyl)-1H-pyrazol-3-yl]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	5.72	92.7	a	571	499
86	N-[(5-{[4-(anilinopiperidin-1-yl)sulfonyl]thien-2-yl)methyl]-4-chlorobenzamide	4.84	91	a	490	488
87	4-chloro-N-[(5-{[4-(3-phenyl-1,2,4-thiadiazol-5-yl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide	6.76	98.7	a	560	558
88	4-chloro-N-[(5-{[4-(2-phenylethyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	7.62	99	a	503	501
89	4-chloro-N-[(5-{[4-(heptylpiperazin-1-yl)sulfonyl]thien-2-yl)methyl]benzamide	5.29	99.1	a	498	496
90	4-chloro-N-[(5-{[4-(octylpiperazin-1-yl)sulfonyl]thien-2-yl)methyl]benzamide	5.59	97.8	a	512	510

Example 91: Preparation of N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide 91

5 **4-(1H-1,2,3-benzotriazol-1-yl)piperidinium trifluoroacetate, 91a**

To a solution of Boc-4-hydroxy-piperidine (201 mg, 1 mmol), Benzotriazole (238mg, 2 mmol) and Triphenylphosphine (523 mg, 2 mmol) in 15 mL THF was added a solution of Diethylazodicarboxylate (326 ul, 2 mmol) in 10 mL THF. The yellow solution was stirred overnight, the solvent was evaporated to dryness and the crude residue was
 10 eluted on silica gel (AcOEt/cyclohexane 7:3). The fractions were isolated containing the 1- and 2-regiosiomers.

Fraction 1 contained the 2-benzotriazole-piperidine isomer (250mg, 82%). ¹H NMR (CDCl₃) δ 7.84 (m, 2H), 7.38 (m, 2H), 4.90 (quint., J = 6.8 Hz.), 4.20 (m, 2H), 3.09 (m, 2H), 2.27 (m, 4H), 1.68 (s, 9H). M/Z APCI: 303.2 (M+1), 247 (M-^tbutyl+1), 203 (M-
 15 Boc+1).

Fraction 2 contained the 1-benzotriazole-piperidine isomer (50 mg, 16%): ¹H NMR (CDCl₃) δ 8.06 (d, J = 8.3 Hz., 1H), 7.92 (d, J = 8.3 Hz, 1H), 7.58 (t, J = 8.3 Hz.), 7.42 (t, J = 8.3 Hz.), 5.25 (m, 1H), 3.52 (m, 2H), 3.20 (m, 2H), 2.55-2.25 (m, 4H), 1.66 (s, 9H). M/Z APCI: 303.2 (M+1), 247 (M-^tbutyl+1), 203 (M-Boc+1).

91a (250 mg, 0.82 mmol) was dissolved in 5 mL CH₂Cl₂. 1mL of TFA was added dropwise and the solution was stirred for 3h. The solvents were evaporated to dryness and the oily residue was precipitated with diethylether to give 240 mg (95%) of XX1:
¹H NMR (DMSO-*d*₆) δ 9.10 (b, m, 1H), 8.72 (b, m, 1H), 8.07 (d, *J* = 8.3 Hz., 1H), 7.96
 5 (d, *J* = 8.3 Hz, 1H), 7.55 (t, *J* = 8.3 Hz.), 7.40 (t, *J* = 8.3 Hz.), 5.25 (m, 1H), 3.52 (m, 2H), 3.20 (m, 2H), 2.55-2.25 (m, 4H), M/Z APCI: 203.2 (M+1).

N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide 91

91 was synthesised according to the protocol for the synthesis of 2. After flash chroma-
 10 tography the main fractions were recrystallized from CH₂Cl₂/Cyclohexane. Isolated yield: 3.1 g (71%). mp.: 174-175°C. ¹H NMR (DMSO-*d*₆) δ 9.41 (t, *J* = 6.0 Hz, 1H), 8.03 (d, *J* = 7.9 Hz, 1H), 7.91 (d, *J* = 8.7 Hz, 2H), 7.87 (d, *J* = 8.7 Hz, 1H), 7.61-7.54 (m, 3H), 7.52 (t, *J* = 8.3 Hz, 1H), 7.39 (t, *J* = 8.3 Hz, 1H), 7.23 (d, *J* = 3.77 Hz, 1H), , 5.01 (m, 1H), 4.70 (d, *J* = 5.6 Hz, 2H), 3.78 (d, *J* = 10.6 Hz, 2H), 2.80-2.64 (m,
 15 2H), 2.34-2.17 (m, 4H). M/Z APCI: 516.2 (M+1), 514.1 (M-1). C₂₃H₂₂ClN₅O₃S₂ Calc.: C: 53.53%. H: 4.30%. N: 13.57%. Found: C: 52.74%, H: 4.29%, N: 13.26%.

Alternatively 3 can be synthesised in a parallel solution phase approach using the protocol applied for 2.

20 The following compounds were prepared on a parallel fashion according to the examples described above

The following table provides HPLC data and mass spectroscopy data of the mentioned examples

Exemple	Name	Rt HPLC	Purity	Gradient HPLC	Mass M+1	Mass M
92	2-(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)-N-(4-chlorophenyl)-acetamide	6.37	91	a	516	514
93	2-{1-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperidin-4-yl}-2H-1,2,3-benzotriazole-5-carboxylic acid	5.62	100	a		
94	4-chloro-N-[(5-{[4-(5-chloro-1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	6.46	99	a	550	548
95	methyl 1-[1-[(5-{[(4-chlorobenzoyl)amino]methyl}-	6.19	83.7	a	574	572

	thien-2-yl)sulfonyl]piperidin-4-yl}-1H-1,2,3-benzotriazole-5-carboxylate					
96	methyl 1-{1-[(5-{[(4-chlorobenzoyl)amino]methyl}-thien-2-yl)sulfonyl]piperidin-4-yl}-1H-1,2,3-benzotriazole-6-carboxylate	6.18	90.5	a	574	572
97	methyl 2-{1-[(5-{[(4-chlorobenzoyl)amino]methyl}-thien-2-yl)sulfonyl]piperidin-4-yl}-2H-1,2,3-benzotriazole-5-carboxylate	6.51	94.5	a	574	572
98	4-chloro-N-[(5-{[4-(6-chloro-1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide	6.53	96	a	550	548
99	4-chloro-N-[(5-{[4-(5-(trifluoromethyl)-1H-1,2,3-benzotriazol-1-yl]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	6.85	94.3	a	584	582
100	N-[(5-{[4-(7-aza-1H-benzimidazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide	4.5	97.6	a	0	514
101	1-{1-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperidin-4-yl}-1H-1,2,3-benzotriazole-5-carboxylic acid	5.46	95.5	a	0	0
102	1-{1-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperidin-4-yl}-1H-1,2,3-benzotriazole-6-carboxylic acid	5.36	97.9	a	0	0
103	N-[(5-{[4-(2-amino-9H-purin-9-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide	4.07	94.6	a	532	530
104	4-chloro-N-[(5-{[4-(9H-purin-9-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	4.67	98.4	a	517	515
105	N-[(5-{[4-(6-amino-9H-purin-9-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide	4.15	91.7	a	532	530
106	4-chloro-N-[(5-{[4-(6-nitro-1H-benzimidazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	5.31	67	a	0	558
107	4-chloro-N-[(5-{[4-(5-nitro-1H-benzimidazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	5.46	86.6	a	560	558
108	4-chloro-N-[(5-{[4-(2H-1,2,3-triazol-2-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	5.77	96.8	a	466	464
109	N-[(5-{[4-(1H-benzimidazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide	4.43	99	a	515	513

Example 110: Preparation of 4-chloro-N-[(5-{[4-[3-propylanilino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide 110

4-(3-propylanilino)piperidine trifluoroacetate salt, 110b

- 5 Boc-piperidin-4-one (2.5g, 12.5 mmol) and 3-propylaniline hydrochloride (2.15g, 12.5 mmol) and 2.1 mL DIEA were stirred in 15 mL DCE for 1h. To this solution acetic acid (750ul, 12.5mmol) and sodium triacetoxyborohydride (3.72g, 17.6mmol) were added and the solution was stirred overnight under Ar. The reaction mixture was diluted with diethylether, and 12mL of NaOH (2N) were added (pH9-10). The organic phase was
- 10 washed twice with brine and dried over MgSO₄. The crude was purified by flash chro-

matography on silica gel using petroleum ether/EtOAc 7:1 as eluant. 3.7 g (94%) of pure **110a** were isolated as a colorless solid. ¹H NMR (DMSO-*d*₆) δ 6.93 (t, *J* = 7.7, 1H), 6.31-6.39 (m, 3H), 5.31 (d, *J* = 8.2, 1H), 3.84 (d, *J* = 13.2 Hz, 2H), 3.33 (m, 1H.), 2.89 (m, 2H), 2.39 (t, *J* = 7.7 Hz, 2H), 1.84 (d *J* = 11.3 Hz, 2H), 1.55 (m, 2H), 1.51 (s, 9H), 1.20 (m, 2H), 0.86 (t, *J* = 7.3 Hz, 3H), M/Z ESI: 319.2 (M+1).

110a (1.5 g, 4.71 mmol) was dissolved in 20 mL CH₂Cl₂. 5 mL of TFA were added dropwise and the solution was stirred for 3h. The solvents were evaporated to dryness and the oily residue was precipitated with diethylether to give 1.45 g (92%) of **110b**.

¹H NMR (DMSO-*d*₆) δ 8.59 (m, 2H), 7.00 (t, *J* = 7.7, 1H), 6.44-6.50 (m, 3H), 3.51 (m, 1H), 3.27 (m, 2H), 3.00 (m, 2H.), 2.42 (t, *J* = 7.7 Hz, 2H), 2.00 (d *J* = 11.3 Hz, 2H), 1.57-1.47 (m, 4H), 0.87 (t, *J* = 7.3 Hz, 3H), M/Z ESI: 219.2 (M+1).

4-chloro-N-{{5-({4-[3-propylanilino]piperidin-1-yl} sulfonyl)thien-2-yl}methyl}-benzamide **110**

110 was synthesised according to the protocol for the synthesis of **2**. After flash chromatography the main fractions were recrystallized from CH₂Cl₂/Cyclohexane. Isolated yield: 430 mg (56%). mp.: 169-170°C. ¹H NMR (DMSO-*d*₆) δ 9.36 (t, *J* = 5.8 Hz, 1H), 7.89 (d, *J* = 8.7 Hz, 2H), 7.56 (d, *J* = 8.7 Hz, 2H), 7.47 (d, *J* = 3.8 Hz, 1H), 7.19 (d, *J* = 3.8 Hz, 1H), 6.90 (t, *J* = 7.5 Hz, 1H), 6.49-6.42 (m, 3H), 5.33 (d, *J* = 7.9 Hz, 1H), 4.68 (d, *J* = 5.6 Hz, 2H), 3.51 (d, *J* = 11.7 Hz, 2H), 3.29 (m, 1H), 2.55 (t, *J* = 10.5 Hz, 2H), 2.36 (t, *J* = 7.3 Hz, 2H), 1.97 (d, *J* = 10.9 Hz, 2H). 1.56-1.37 (m, 4H), 0.84 (t, *J* = 7.3 Hz, 3H). M/Z APCI: 532.2 (M+1), 530.1 (M-1). C₂₆H₃₀ClN₃O₃S₂ Calc.: C: 58.70%. H: 5.68%. N: 7.90%. Found: C: 58.55%, H: 5.67%, N: 7.93%.

Alternatively **110** can be synthesised in a parallel solution phase approach:

In a 4 ml Alltech[®] tube 1 eq. of piperidine trifluoroacetate salt is shaken with polymer-bound NMM (4eq.) in 1.2 mL CH₂Cl₂/DMF. After 15 min 1 mL of a stock solution of **1b** in CH₂Cl₂/DMF (1.2eq.) is added and the reaction slurry is shaken. After 3h Aminomethyl Merryfield resin (0.4 eq) is added and the reaction is shaken overnight. Occasionally remaining amine is removed with polymerbound isocyanate (0.2 eq.). The slurry is again shaken for 1h. The solution is filtered off, the resins are washed 3 x with



CH₂Cl₂, and the solvents are evaporated at medium temperature in a Savant Speed Vac® Plus vacuum centrifuge for 1h.

The following compounds were prepared on a parallel fashion according to the examples described above

The following table provides HPLC data and mass spectroscopy data of the mentioned examples

10

Exemple	Name	Rt HPLC	Purity	Gradient HPLC	Mass M+1	Mass M
111	4-chloro-N-([5-(4-[3-(trifluoromethyl)anilino]-piperidin-1-yl)sulfonyl]thien-2-yl)methyl)-benzamide	7.4	96	a	558	556
112	4-chloro-N-([5-(4-[3-(dimethylamino)anilino]-piperidin-1-yl)sulfonyl]thien-2-yl)methyl)-benzamide	4.86	94.8	a	533	531
113	methyl 3-([1-([5-([4-chlorobenzoyl]amino)-methyl]thien-2-yl)sulfonyl]piperidin-4-yl)amino)-benzoate	6.33	96.6	a	548	546
114	4-chloro-N-([5-(4-[3-(methylsulfonyl)anilino]-piperidin-1-yl)sulfonyl]thien-2-yl)methyl)-benzamide	6.07	97.4	a	536	534
115	4-chloro-N-([5-(4-[3-nitroanilino]piperidin-1-yl)sulfonyl]thien-2-yl)methyl)benzamide	6.93	88.3	a	535	533
116	4-chloro-N-([5-(4-[2-methoxyanilino]piperidin-1-yl)sulfonyl]thien-2-yl)methyl)benzamide	5.12	96.2	a	520	518
117	3-([1-([5-([4-chlorobenzoyl]amino)methyl]thien-2-yl)sulfonyl]piperidin-4-yl)amino)benzamide	4.52	69	a	533	531
118	4-chloro-N-([5-(4-[2-(trifluoromethyl)anilino]-piperidin-1-yl)sulfonyl]thien-2-yl)methyl)-benzamide	7.7	97.5	a	558	556
119	4-chloro-N-([5-(4-[2-nitro-4-(trifluoromethyl)sulfonyl]anilino]piperidin-1-yl)sulfonyl]thien-2-yl)methyl)benzamide	7.55	84.8	a	667	665
120	4-chloro-N-([5-(4-[4-(4-chloroanilino)piperidin-1-yl)sulfonyl]thien-2-yl)methyl)benzamide	6.6	86.2	a	524	522
121	4-chloro-N-([5-(4-[4-(trifluoromethyl)anilino]-piperidin-1-yl)sulfonyl]thien-2-yl)methyl)-benzamide	7.45	96.8	a	558	556
122	4-chloro-N-([5-(4-[4-(trifluoromethyl)sulfonyl]anilino]piperidin-1-yl)sulfonyl]thien-2-yl)methyl)-benzamide	7.3	95.5	a	622	620
123	4-chloro-N-([5-(4-[2-nitroanilino]piperidin-1-yl)sulfonyl]thien-2-yl)methyl)benzamide	7.13	92.8	a	535	533
124	N-([5-(4-[4-(aminocarbonyl)anilino]piperidin-1-yl)sulfonyl]thien-2-yl)methyl)-4-chlorobenzamide	4.9	74	a	533	531
125	4-chloro-N-([5-(4-[4-(1,3-dithiolan-2-yl)anilino]-piperidin-1-yl)sulfonyl]thien-2-yl)methyl)-	6.2	94.2	a	594	0

	benzamide					
126	N-[(5-{[4-(3-chloroanilino)piperidin-1-yl]sulfonyl}-thien-2-yl)methyl]-3-nitrobenzamide	6.68	97.8	a	535	533
127	4-chloro-N-[(5-{[4-(3-chloroanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	7.06	93.9	a	524	522
128	4-chloro-N-[(5-{[4-(3-methoxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	5.4	92	a	519	517
129	4-chloro-N-[(5-{[4-(3-(methylsulfonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl)methyl]-benzamide	6.06	91.7	a	568	566
130	N-[(5-{[4-(3-[amino(imino)methyl]anilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide	4.3	91.4	a	532	530
131	4-chloro-N-[(5-{[4-(3-[(2-hydroxyethyl)sulfonyl]anilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide	5.16	92.3	a	598	596
132	N-[(5-{[4-(2-aminoanilino)piperidin-1-yl]sulfonyl}-thien-2-yl)methyl]-4-chlorobenzamide	4.63	78	a	506	504
133	4-chloro-N-[(5-{[4-(2-hydroxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	4.47	94.3	a	506	504
134	4-chloro-N-[(5-{[4-(4-hydroxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	4.3	86.8	a	506	504
135	4-chloro-N-[(5-{[4-(3-[(trifluoromethyl)sulfonyl]anilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide	7.1	89.1	a	590	588
136	4-chloro-N-[(5-{[4-(3-toluidino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	4.73	85.3	a	504	502
137	4-chloro-N-[(5-{[4-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)amino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	7.58	99	a	593	591
138	4-chloro-N-[(5-{[4-(3-(1,3-oxazol-5-yl)anilino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide	5.68	86.5	a	557	555
139	N-[(5-{[4-(3-tert-butylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide	5.77	98	a	546	544
140	4-chloro-N-[(5-{[4-(2-propylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	6.42	96.1	a	532	530
141	4-chloro-N-[(5-{[4-(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)amino]piperidin-1-yl]sulfonyl}-thien-2-yl)methyl]benzamide	5.47	95	a	580	578
142	4-chloro-N-[(5-{[4-(2,3-dihydro-1H-inden-5-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide	5.15	97.4	a	530	528
143	4-chloro-N-[(5-{[4-(4-propylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	5.49	98.7	a	532	530
144	4-chloro-N-[(5-{[4-(3-nitropyridin-2-yl)amino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide	6.62	99.3	a	537	535
145	N-[(5-{[4-(3-aminopyridin-2-yl)amino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide	4.37	96.1	a	506	504
146	N-[(5-{[4-(1,1'-biphenyl)-3-ylamino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide	6.25	92.4	a	566	564
147	N-[(5-{[4-(3-benzylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide	7.29	96.1	a	589	587
148	4-chloro-N-[(5-{[4-(pyrimidin-2-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	4.55	97.7	a	492	490

149	4-chloro-N-([5-([4-[4-(morpholin-4-ylsulfonyl)-anilino]piperidin-1-yl)sulfonyl]thien-2-yl)methyl]-benzamide	6.2	96.2	a	639	637
150	4-chloro-N-([5-([4-([4-(trifluoromethyl)pyrimidin-2-yl]amino)piperidin-1-yl)sulfonyl]thien-2-yl)methyl]benzamide	6.06	94.2	a	560	558
151	4-chloro-N-([5-([4-(3-cyclohexyl-4-hydroxyanilino)piperidin-1-yl)sulfonyl]thien-2-yl)methyl]benzamide	5.01	85.2	a	588	586
152	N-([5-([4-([3-[(butylamino)sulfonyl]anilino)-piperidin-1-yl)sulfonyl]thien-2-yl)methyl]-4-chlorobenzamide	6.05	99.7	a	626	624
153	4-chloro-N-([5-([4-(3-ethylanilino)piperidin-1-yl)sulfonyl]thien-2-yl)methyl]benzamide	4.86	98.4	a	518	516
154	4-chloro-N-([5-([4-(5,6,7,8-tetrahydronaphthalen-1-ylamino)piperidin-1-yl)sulfonyl]thien-2-yl)methyl]benzamide	5.36	86.9	a	544	542
155	N-([5-([4-([3-(aminosulfonyl)anilino]piperidin-1-yl)sulfonyl]thien-2-yl)methyl]-4-chlorobenzamide	5.57	98.9	a	0	566
156	4-chloro-N-([5-([4-(quinolin-5-ylamino)piperidin-1-yl)sulfonyl]thien-2-yl)methyl]benzamide	4.57	95.8	a	541	539
157	4-chloro-N-([5-([4-(quinolin-8-ylamino)piperidin-1-yl)sulfonyl]thien-2-yl)methyl]benzamide	5.65	97	a	541	539

Example 158: Preparation of 4-Chloro-N-([5-([4-(3-propylphenoxy)piperidin-1-yl)sulfonyl]thien-2-yl)methyl]benzamide 158

4-(3-propylphenoxy)piperidinium trifluoroacetate, 158a

To a solution of Boc-4-hydroxy-piperidine (1g, 4.97mmol), 3-propylphenol (677mg, 4.97 mmol) and Triphenylphosphine (1.304g, 4.97 mmol) in 30 mL THF was added a solution of Diethylazodicarboxylate (866 mg, 4.97 mmol) in 10 mL THF. The yellow solution was stirred overnight, the solvent was evaporated to dryness and the crude residue was eluted on silica gel (AcOEt/cyclohexane 1:9) to provide 880 mg (56%) of pure 158a.

158a was dissolved in 10 mL CH₂Cl₂ and 2 mL TFA were added. After 3h the reaction mixture was evaporated to dryness and the residual oil was precipitated with diethyl-ether to afford 800mg (92%) of pure TFA salt 158a: ¹H NMR (DMSO-*d*₆) δ 8.42 (b, m, 2H), 7.04 (d, *J* = 7.7 Hz, 1H), 6.65 (m, 3H), 4.47 (m, 1H), 3.20-2.80 (b, m, 4H), 2.46 (m, 2H), 1.90 (m, 2H), 1.65 (m, 2H), 1.43 (m, 2H), 0.74 (t, *J* = 7.3 Hz, 3H).



4-Chloro-N-[(5-{[4-(3-propylphenoxy)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide 158

158 was synthesised according to the protocol for the synthesis of 2. After flash chromatography the main fractions were recrystallized from CH₂Cl₂/Cyclohexane. Isolated
 5 yield: 24 mg (88%). ¹H NMR (DMSO-*d*₆) δ 9.38 (t, *J* = 5.6 Hz, 1H), 7.90 (d, *J* = 8.7 Hz, 2H), 7.56 (d, *J* = 8.7 Hz, 2H), 7.50 (d, *J* = 3.7 Hz, 1H), 7.19 (d, *J* = 3.7 Hz, 1H), 7.09 (t, *J* = 8.1 Hz, 1H), 6.85-6.66 (m, 3H), 4.68 (d, *J* = 5.6 Hz, 2H), 3.51 (d, *J* = 11.7 Hz, 2H), 3.29 (m, 1H), 2.87 (t, *J* = 10.5 Hz, 2H), 2.45 (t, *J* = 7.3 Hz, 2H), 2.00 (d, *J* = 10.9 Hz, 2H), 1.56-1.37 (m, 4H), 0.84 (t, *J* = 7.2 Hz, 3H). M/Z APCI: 533.2 (M+1),
 10 531.1 (M-1).

Protocol #2

Example 159 : Preparation of 4-chloro-N-{[5-(4-[(2E)-3-phenylprop-2-enoyl]piperazin-1-yl)sulfonyl]thien-2-yl)methyl}benzamide 159

15 To a stirred solution of 1 (36 mg, 0.09 mmol) and iPr₂NEt (32 μ l, 0.189 mmol) in CHCl₃ (2 mL) was added [(2E)-3-phenylprop-2-enoyl]chloride (15 mg, 0.09 mmol). After 4 h the reaction mixture was washed with HCl (1 N) and sat. NaCl solution, and dried over MgSO₄. The solvent was evaporated and the residue was filtered through
 20 silica gel using AcOEt/MeOH 1% as eluent to afford 159 as white solid (10 mg, 20%). M/Z APCI: 531.2 (M+1), 529.1 (M-1). Anal. HPLC: rt. = 6.18 min (method a).

The following compounds were prepared on a parallel fashion according to the examples described above

25 The following table provides HPLC data and mass spectroscopy data of the mentioned examples

Exemple	Name	Rt HPLC	Purity	Gradient HPLC	Mass M+1	Mass M
160	4-chloro-N-({5-[(4-{4-nitrobenzoyl}piperazin-1-yl)sulfonyl]thien-2-yl)methyl}benzamide	12.75	96	b	549	547
161	N-({5-[(4-benzoylpiperazin-1-yl)sulfonyl]thien-2-yl)methyl}-4-chlorobenzamide		85	b	504	502
162	4-chloro-N-({5-[(4-{4-(trifluoromethyl)benzoyl}piperazin-1-yl)sulfonyl]thien-2-yl)methyl}-benzamide		98	b	572	570

163	4-chloro-N-{{5-({4-[4-(dimethylamino)benzoyl]-piperazin-1-yl} sulfonyl)thien-2-yl}methyl}-benzamide		93	b	547	545
164	4-chloro-N-{{5-({4-(2-fluorobenzoyl)piperazin-1-yl} sulfonyl)thien-2-yl}methyl}benzamide		98	b	522	520
165	4-chloro-N-{{5-({4-(2,6-difluorobenzoyl)piperazin-1-yl} sulfonyl)thien-2-yl}methyl}benzamide		96	b	540	538
166	4-chloro-N-{{5-({4-(3-fluorobenzoyl)piperazin-1-yl} sulfonyl)thien-2-yl}methyl}benzamide		93	b	522	520
167	4-chloro-N-{{5-({4-(2-naphthoyl)piperazin-1-yl} sulfonyl)thien-2-yl}methyl}benzamide	13.6	90	b	554	552
168	4-chloro-N-{{5-({4-(1-naphthoyl)piperazin-1-yl} sulfonyl)thien-2-yl}methyl}benzamide	13.44	93	b	554	552
169	4-chloro-N-{{5-({4-(2-nitrobenzoyl)piperazin-1-yl} sulfonyl)thien-2-yl}methyl}benzamide	12.26	87	b	549	547
170	4-chloro-N-{{5-({4-(pyridin-3-ylcarbonyl)piperazin-1-yl} sulfonyl)thien-2-yl}methyl}benzamide	9.17	84	b	505	503
171	N-{{5-({4-(2,1,3-benzoxadiazol-5-ylcarbonyl)piperazin-1-yl} sulfonyl)thien-2-yl}methyl}-4-chlorobenzamide	12.75	99	b	546	544
172	4-chloro-N-{{5-({4-(2,4-difluorobenzoyl)piperazin-1-yl} sulfonyl)thien-2-yl}methyl}benzamide	12.84	90	b	540	538
173	4-chloro-N-{{5-({4-(2,4,6-trifluorobenzoyl)piperazin-1-yl} sulfonyl)thien-2-yl}methyl}-benzamide	13.06	89	b	558	556
174	4-chloro-N-{{5-({4-(2,6-dichlorobenzoyl)piperazin-1-yl} sulfonyl)thien-2-yl}methyl}benzamide	13.19	95	b	574	572
175	4-chloro-N-{{5-({4-(heptanoyl)piperazin-1-yl} sulfonyl)thien-2-yl}methyl}benzamide	6.35	99.4	a	512	510
176	4-chloro-N-{{5-({4-(quinolin-8-ylsulfonyl)piperazin-1-yl} sulfonyl)thien-2-yl}methyl}benzamide	5.86	93.6	a	591	589

Protocol #3

Example 177: Preparation of 4-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}-piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide 177

5

{{(3-Nitrobenzoyl)amino}methyl}thiophene-2-sulfonyl chloride 177a

To a solution of 2-Aminomethylthiophene (10.6mL, 103mmol) and pyridine (9.1mL, 104mmol) in 100mL of chloroform was added at 0°C a solution of 3-Nitrobenzoyl-chloride (19.2g, 103mmol) in CH₂Cl₂. The reaction was allowed to warm to rt. during 1h and stirred for additional 3h. Water was added while 3-Nitro-N-(thien-2-ylmethyl)-benzamide (10.1g) precipitated. The solid was filtered off and washed with water. The remaining organic layer was washed with brine, dried over MgSO₄ and evaporated to dryness to afford additional 3-Nitro-N-(thien-2-ylmethyl)benzamide (15.2g). The overall yield was 25.3 g (99.9%). 3-Nitro-N-(thien-2-ylmethyl)benzamide was used for the next step without further purification.

15

Chlorosulfonic acid (5.62mL, 84mmol) was dissolved in 20mL CH₂Cl₂ and added to a solution of 3-Nitro-*N*-(thien-2-ylmethyl)benzamide (11.0g, 42mmol) in 100mL CH₂Cl₂ under vigorous stirring. A gummy solid was formed and the reaction mixture was stirred for 3h. The reaction was quenched with ice, and ice cold NaHCO₃ solution was added to reach pH8.5. The aqueous layer was washed twice with CH₂Cl₂. Tetrabutylammoniumhydroxide (40% in water) (32mL, 50mmol) was added to the aqueous layer, while a solid was formed. The precipitate was extracted into CH₂Cl₂ and the aqueous layer was washed 3x with CH₂Cl₂. The combined organic layers were dried over MgSO₄ and evaporated to dryness to afford a slightly colored foam of Tetrabutylammonium 5-[[3-Nitrobenzoyl]amino]methyl}thiophene-2-sulfonate (24g, 97%). NMR spectra indicated pure compound, which was used for the following chlorination step.

To a solution of Tetrabutylammonium 5-[[3-Nitrobenzoyl]amino]methyl}thiophene-2-sulfonate (2.0g, 3.4mmol) in 50mL CH₂Cl₂ was added triphosgene (800mg, 2.7mmol, 2.3eq.), dissolved in 10mL CH₂Cl₂. To this reaction mixture DMF (0.1mL, 1.4mmol) was added dropwise during 10', while gas evolution could be observed. The gases were trapped at the outlet of the reaction flask in a 2N NaOH solution. The reaction mixture was stirred for 3h, and the crude was directly filtered through silica gel using EtOAc/hexane 1:2 as eluent. An orange solid could be isolated which was recrystallised from cyclohexane/ CH₂Cl₂. **177a** (730mg, 60%) was obtained as colorless needles. ¹H NMR (CDCl₃) δ 8.83 (t, *J* = 1.5 Hz, 1H), 8.35 (t, *J* = 7.5Hz, 1H), 7.76 (t, *J* = 4.1 Hz, 1H), 7.70-7.58 (m, 3H), 7.52-7.40 (m, 2H), 7.05 (t, *J* = 3.8 Hz, 1H).

3-Nitro-*N*-({5-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide **177**

A suspension of the sulfonyl chloride **177a** (573 mg, 1.58 mmol), 4-(3-trifluoromethanesulfonyl-phenylamino)-piperidine (490 mg, 1.58 mmol), and Et₃N (330 ul, 2.38 mmol) in CH₂Cl₂ (30 mL) was stirred for 3h at 23°C, whereupon the suspension turned to a clear solution. The standard work-up (HCl 1N; brine; MgSO₄) gave the crude product as a yellow foam. This was dissolved in DMSO (1 mL) and CH₃CN (3 mL), and injected on a reverse-phase prep. HPLC (C8, gradient H₂O:CH₃CN 60:40 → 0:100 over

40 min, retention time = 20 min). Freeze-drying of the desired fractions afforded 667 mg (67%) of the title sulfonamide as a pale yellow powder: ^1H NMR (DMSO- d_6) δ 9.69 (t, J = 5.8 Hz, 1H), 8.72 (t, J = 1.9 Hz, 1H), 8.41 (dd, J = 8.3, 1.9 Hz, 1H), 8.34 (d, J = 7.9 Hz, 1H), 7.81 (t, J = 8.1 Hz, 1H), 7.50 (d, J = 3.8 Hz, 1H), 7.45 (t, J = 7.9 Hz, 1H), 7.23 (d, J = 3.8 Hz, 1H), 7.15–7.11 (m, 3H), 6.52 (d, J = 7.9 Hz, 1H), 4.73 (d, J = 5.7 Hz, 2H), 3.57–3.42 (br. d, J = 11.7 Hz, 2H), 3.52–3.33 (m, 1H), 2.62 (t, J = 10.4 Hz, 2H), 2.00–1.90 (br. d, J = 10.6 Hz), 1.43 (qd, J \approx 10.2, 3 Hz, 2H). ^{13}C NMR (DMSO- d_6) δ 164.66 (s, C=O), 150.51 (s), 149.32 (s), 148.20 (s), 135.30 (s), 134.22 (s), 134.11 (d), 132.98 (d), 131.49 (d), 130.67 (d), 130.44 (s), 127.00 (d), 126.60 (d), 122.38 (d), 120.41 (d), 119.81 (q, J = 326 Hz, CF_3), 116.72 (d), 112.79 (d), 47.43 (d), 45.15 (t), 38.58 (t), 30.66 (t). M/Z APCI : 633 (M+1), 631 (M–1). Anal. HPLC: R_t = 6.41 min (method a). $\text{C}_{24}\text{H}_{23}\text{F}_3\text{N}_4\text{O}_7\text{S}_3$ Calc.: C: 45.56%. H: 3.66%. N: 8.86%. Found: C: 45.30%, H: 3.73%, N: 8.85%.

In the here-described sequence, the 3-nitrobenzoyl chloride initially used could be replaced with other acylating reagents, which include (but are not limited to): 4-nitrobenzoyl, 4-chlorobenzoyl chloride, 3-methoxybenzoylchloride, trifluoroacetic anhydride.

The following compounds were prepared on a parallel fashion according to the examples described above

The following table provides HPLC data and mass spectroscopy data of the mentioned examples

Exemple	Name	R _t HPLC	Purity	Gradient HPLC	Mass M+1	Mass M
178	N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide	5.62	63.1	a	527	525
179	4-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl)methyl}-benzamide	6.77	87.3	a	633	631
180	N-[(5-{[4-(2,4-difluorobenzoyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide	6.3	92.7	a	550	548
181	N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide	5.6	77.3	a	527	525
182	N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide	5.62	63.1	a	527	525
183	4-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl)methyl}-benzamide	6.77	87.3	a	633	631
184	N-[(5-{[4-(2,4-difluorobenzoyl)piperidin-1-yl]-	6.3	92.7	a	550	548

	sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide					
185	N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide	5.6	77.3	a	527	525
186	3-nitro-N-[(5-{[4-(3-methoxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	4.86	88.3	a	533	531
187	3-nitro-N-[(5-{[4-[3-(trifluoromethyl)anilino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide	7.03	91	a	568	566
188	N-[(5-{[4-[3-(dimethylamino)anilino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide	4.2	97.5	a	544	542
189	3-nitro-N-[(5-{[4-[3-(methylsulfonyl)anilino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide	5.71	91.4	a	579	0
190	3-nitro-N-[(5-{[4-[3-(methylsulfonyl)anilino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide	5.64	92.2	a	547	0
191	N-[(5-{[4-[3-(aminosulfonyl)anilino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide	5.32	63	a	580	0
192	methyl 3-[(1-{[5-{[3-nitrobenzoyl]amino}methyl]thien-2-yl}sulfonyl)-piperidin-4-yl]amino benzoate	5.89	88.3	a	559	557
193	N-[(5-{[4-[3-(aminocarbonyl)anilino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide	4.44	65.2	a	0	542
194	3-nitro-N-[(5-{[4-[3-nitroanilino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	6.53	88.4	a	546	544
195	3-nitro-N-[(5-{[4-(2-methoxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	4.71	86.1	a	532	530
196	3-nitro-N-[(5-{[4-[2-(trifluoromethyl)anilino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide	7.23	94.5	a	569	567
197	3-nitro-N-[(5-{[4-[2-nitroanilino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	6.68	91.4	a	546	544
198	N-[(5-{[4-(4-chloroanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide	6.12	94.7	a	535	533
199	3-nitro-N-[(5-{[4-[4-(trifluoromethyl)anilino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide	7.09	91.3	a	569	567
200	3-nitro-N-[(5-{[4-[4-(trifluoromethyl)sulfonyl]anilino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide	6.92	92.4	a	633	631
201	N-[(5-{[4-[4-(aminocarbonyl)anilino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide	4.91	61.1	a	544	542
202	N-[(5-{[4-(3-propylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide	5.44	81.3	a	543	541
203	N-[(5-{[4-(3-chloroanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide	6.18	92.5	a	535	533
204	4-nitro-N-[(5-{[4-(3-methoxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	5.01	97	a	531	529
205	4-nitro-N-[(5-{[4-[3-(trifluoromethyl)anilino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide	6.98	97.1	a	569	567
206	N-[(5-{[4-[3-(dimethylamino)anilino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide	4.23	89.7	a	544	542
207	4-nitro-N-[(5-{[4-(3-propylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	5.44	97.5	a	543	541
208	4-nitro-N-[(5-{[4-[3-(methylsulfonyl)anilino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-	5.36	92.1	a	579	577

	benzamide					
209	4-nitro-N-([5-(4-[3-(methylsulfonyl)anilino]piperidin-1-yl)sulfonyl]thien-2-yl)methyl]-benzamide	5.29	90.1	a	547	545
210	N-([5-(4-[3-(aminosulfonyl)anilino]piperidin-1-yl)sulfonyl]thien-2-yl)methyl]-4-nitrobenzamide	4.96	90.8	a	580	578
211	methyl 3-([1-(5-([4-nitrobenzoyl]amino)methyl]thien-2-yl)sulfonyl]piperidin-4-yl)amino}benzoate	5.5	99	a	559	557
212	3-([1-(5-([4-nitrobenzoyl]amino)methyl]thien-2-yl)sulfonyl]piperidin-4-yl)amino}benzamide	4.4	87	a	544	542
213	4-nitro-N-([5-(4-[3-nitroanilino]piperidin-1-yl)sulfonyl]thien-2-yl)methyl]benzamide	6.13	86.3	a	546	544
214	4-nitro-N-([5-(4-[2-methoxyanilino]piperidin-1-yl)sulfonyl]thien-2-yl)methyl]benzamide	4.4	97.8	a	531	529
215	4-nitro-N-([5-(4-[2-(trifluoromethyl)anilino]piperidin-1-yl)sulfonyl]thien-2-yl)methyl]-benzamide	6.76	97.7	a	569	567
216	4-nitro-N-([5-(4-[2-nitroanilino]piperidin-1-yl)sulfonyl]thien-2-yl)methyl]benzamide	6.66	99.5	a	546	544
217	N-([5-(4-[4-chloroanilino]piperidin-1-yl)sulfonyl]thien-2-yl)methyl]-4-nitrobenzamide	6.11	99	a	535	533
218	4-nitro-N-([5-(4-[4-(trifluoromethyl)anilino]piperidin-1-yl)sulfonyl]thien-2-yl)methyl]-benzamide	6.62	94.7	a	569	567
219	4-nitro-N-([5-(4-[4-(trifluoromethyl)sulfonyl]anilino]piperidin-1-yl)sulfonyl]thien-2-yl)methyl]-benzamide	6.48	96.8	a	633	631
220	N-([5-(4-[4-(aminocarbonyl)anilino]piperidin-1-yl)sulfonyl]thien-2-yl)methyl]-4-nitrobenzamide	4.92	96.7	a	543	541
221	N-([5-(4-[4-(1,3-dithiolan-2-yl)anilino]piperidin-1-yl)sulfonyl]thien-2-yl)methyl]-4-nitrobenzamide	5.41	92.4	a	605	603
222	N-([5-(4-[3-[amino(imino)methyl]anilino]piperidin-1-yl)sulfonyl]thien-2-yl)methyl]-3-nitrobenzamide	4.24	90.4	a	543	541
223	N-([5-(4-[3-[(2-hydroxyethyl)sulfonyl]anilino]piperidin-1-yl)sulfonyl]thien-2-yl)methyl)-3-nitrobenzamide	5.22	94.7	a	610	608
224	N-([5-(4-[4-anilinopiperidin-1-yl)sulfonyl]thien-2-yl)methyl)-3-nitrobenzamide	4.35	87.9	a	501	499
225	N-([5-(4-[3-[(2-hydroxyethyl)sulfonyl]anilino]piperidin-1-yl)sulfonyl]thien-2-yl)methyl)-4-nitrobenzamide	4.91	94	a	610	608
226	N-([5-(4-[4-anilinopiperidin-1-yl)sulfonyl]thien-2-yl)methyl)-4-nitrobenzamide	4.34	94.4	a	501	499
227	N-([5-(4-[3-[amino(imino)methyl]anilino]piperidin-1-yl)sulfonyl]thien-2-yl)methyl)-4-nitrobenzamide	4.23	90.8	a	543	541
228	3-nitro-N-([5-(4-[3-[(trifluoromethyl)sulfonyl]anilino]piperidin-1-yl)sulfonyl]thien-2-yl)methyl)-benzamide	7.23	88	a	601	599
229	4-nitro-N-([5-(4-[3-[(trifluoromethyl)sulfonyl]anilino]piperidin-1-yl)sulfonyl]thien-2-yl)methyl)-benzamide	7.28	90.4	a	601	599
230	3-nitro-N-([5-(4-[3-nitropyridin-2-yl]amino]piperidin-1-yl)sulfonyl]thien-2-yl)methyl]-benzamide	6.35	95.8	a	547	545

231	N-{{5-{{4-{{(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)amino}piperidin-1-yl}sulfonyl}thien-2-yl)methyl}-3-nitrobenzamide	5.18	94.5	a	591	589
232	N-{{5-{{4-{{(2,3-dihydro-1H-inden-5-ylamino)-piperidin-1-yl}sulfonyl}thien-2-yl)methyl}-3-nitrobenzamide	4.88	92	a	541	539
233	3-nitro-N-{{5-{{4-{{(2-propylanilino)piperidin-1-yl}sulfonyl}thien-2-yl)methyl}benzamide	6.14	90.2	a	543	541
234	3-nitro-N-{{5-{{4-{{(4-propylanilino)piperidin-1-yl}sulfonyl}thien-2-yl)methyl}benzamide	5.23	93.2	a	543	541
235	N-{{5-{{4-{{(3-tert-butylanilino)piperidin-1-yl}sulfonyl}thien-2-yl)methyl}-3-nitrobenzamide	5.5	94.4	a	557	555
236	3-nitro-N-{{5-{{4-{{(3-(1,3-oxazol-5-yl)anilino)-piperidin-1-yl}sulfonyl}thien-2-yl)methyl}-benzamide	5.44	91.1	a	568	566
237	3-nitro-N-{{5-{{4-{{(2-phenylethyl)piperidin-1-yl}sulfonyl}thien-2-yl)methyl}benzamide	7.36	97.5	a	514	512
238	N-{{5-{{4-{{(3-chloro-5-(trifluoromethyl)pyridin-2-yl)amino}piperidin-1-yl}sulfonyl}thien-2-yl)methyl}-3-nitrobenzamide	7.27	90.3	a	604	602
239	N-{{5-{{4-{{(1,1'-biphenyl)-3-ylamino}piperidin-1-yl}sulfonyl}thien-2-yl)methyl}-3-nitrobenzamide	5.97	82.3	a	577	575
240	N-{{5-{{4-{{(3-benzylanilino)piperidin-1-yl}sulfonyl}thien-2-yl)methyl}-3-nitrobenzamide	5.86	69	a	591	589
241	3-nitro-N-{{5-{{4-{{(3-(morpholin-4-ylsulfonyl)-anilino)piperidin-1-yl}sulfonyl}thien-2-yl)methyl}-benzamide	5.92	96.4	a	650	648
242	3-nitro-N-{{5-{{4-{{(3-propylphenoxy)piperidin-1-yl}sulfonyl}thien-2-yl)methyl}benzamide	7.56	75	a	544	542
243	4-nitro-N-{{5-{{4-{{(pyrimidin-2-ylamino)piperidin-1-yl}sulfonyl}thien-2-yl)methyl}benzamide	4.28	92	a	503	501
244	N-{{5-{{4-{{(3-aminopyridin-2-yl)amino}piperidin-1-yl}sulfonyl}thien-2-yl)methyl}-4-nitrobenzamide	4.06	90	a	517	515
245	4-nitro-N-{{5-{{4-{{(3-nitropyridin-2-yl)amino)-piperidin-1-yl}sulfonyl}thien-2-yl)methyl}-benzamide	6.31	94.3	a	547	545
246	N-{{5-{{4-{{(2,3-dihydro-1H-inden-5-ylamino)-piperidin-1-yl}sulfonyl}thien-2-yl)methyl}-4-nitrobenzamide	4.92	89.9	a	541	539
247	4-nitro-N-{{5-{{4-{{(2-propylanilino)piperidin-1-yl}sulfonyl}thien-2-yl)methyl}benzamide	6.17	93.9	a	543	541
248	4-nitro-N-{{5-{{4-{{(4-propylanilino)piperidin-1-yl}sulfonyl}thien-2-yl)methyl}benzamide	5.27	93.8	a	543	541
249	N-{{5-{{4-{{(3-tert-butylanilino)piperidin-1-yl}sulfonyl}thien-2-yl)methyl}-4-nitrobenzamide	5.54	92.7	a	557	555
250	4-nitro-N-{{5-{{4-{{(3-(1,3-oxazol-5-yl)anilino)-piperidin-1-yl}sulfonyl}thien-2-yl)methyl}-benzamide	5.43	94.3	a	568	566
251	4-nitro-N-{{5-{{4-{{(2-phenylethyl)piperidin-1-yl}sulfonyl}thien-2-yl)methyl}benzamide	7.32	97.9	a	514	512
252	N-{{5-{{4-{{(3-chloro-5-(trifluoromethyl)pyridin-2-yl)amino}piperidin-1-yl}sulfonyl}thien-2-yl)methyl}-4-nitrobenzamide	7.29	86.1	a	604	602
253	N-{{5-{{4-{{(1,1'-biphenyl)-3-ylamino}piperidin-1-yl}sulfonyl}thien-2-yl)methyl}-4-nitrobenzamide	6	85.2	a	577	575
254	N-{{5-{{4-{{(3-benzylanilino)piperidin-1-yl}sulfonyl}-	5.9	90.4	a	591	589

	thien-2-yl)methyl]-4-nitrobenzamide					
255	4-nitro-N-{{5-({4-[3-(morpholin-4-ylsulfonyl)-anilino]piperidin-1-yl)sulfonyl}thien-2-yl)methyl}-benzamide	5.95	95.5	a	650	648
256	N-{{5-({4-(2-aminoanilino)piperidin-1-yl)sulfonyl}thien-2-yl)methyl}-3-nitrobenzamide	4.37	75.6	a	516	514
257	3-nitro-N-{{5-({4-(pyrimidin-2-ylamino)piperidin-1-yl)sulfonyl}thien-2-yl)methyl}benzamide	4.24	89.1	a	503	501
258	N-{{5-({4-[(3-aminopyridin-2-yl)amino]piperidin-1-yl)sulfonyl}thien-2-yl)methyl}-3-nitrobenzamide	4.03	80	a	517	515
259	N-{{5-({4-[2-nitro-4-[(trifluoromethyl)sulfonyl]-anilino]piperidin-1-yl)sulfonyl}thien-2-yl)methyl}-3-methoxybenzamide	6.66	96.8	a	690	988
259	ethyl 5-{{[(3-methoxybenzoyl)amino]methyl}-2-{{4-{{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl}thiophene-3-carboxylate	6.66	96.8	a	690	988
260	3-nitro-N-{{5-({4-(3-phenylpropyl)piperazin-1-yl)sulfonyl}thien-2-yl)methyl}benzamide	4.41	99.3	a	529	527
261	3-nitro-N-{{5-({4-{{4-(trifluoromethyl)pyrimidin-2-yl}amino}piperidin-1-yl)sulfonyl}thien-2-yl)methyl}benzamide	5.78	99.3	a	571	569
262	N-{{5-({4-(3-cyclohexyl-4-hydroxyanilino)-piperidin-1-yl)sulfonyl}thien-2-yl)methyl}-3-nitrobenzamide	4.78	81	a	599	597
263	N-{{5-({4-{{3-[(butylamino)sulfonyl]anilino}-piperidin-1-yl)sulfonyl}thien-2-yl)methyl}-3-nitrobenzamide	5.8	99.4	a	636	634
264	N-{{5-({4-(3-ethylanilino)piperidin-1-yl)sulfonyl}thien-2-yl)methyl}-3-nitrobenzamide	4.64	97.6	a	529	527
265	3-nitro-N-{{5-({4-(5,6,7,8-tetrahydronaphthalen-1-ylamino)piperidin-1-yl)sulfonyl}thien-2-yl)methyl}-benzamide	5.13	88.5	a	555	553
266	4-nitro-N-{{5-({4-(3-propylphenoxy)piperidin-1-yl)sulfonyl}thien-2-yl)methyl}benzamide	7.57	75.8	a	544	542
267	N-{{5-({4-(2,4-difluorobenzoyl)piperidin-1-yl)sulfonyl}thien-2-yl)methyl}-3-nitrobenzamide	6.33	97.7	a	550	553

Protocol #4

Example 268: Preparation of N-{{5-{{4-(2,4-difluorobenzoyl)piperidin-1-yl)sulfonyl}thien-2-yl)methyl}-3-methoxybenzamide 268

5

[[3-(Methoxybenzoyl)amino]methyl]thiophene-2-sulfonyl chloride 268a

The title sulfonylchloride was prepared according to the synthetic **protocol#3** (example 177).

After flash chromatography using cyclohexane/EtOAc 1:1 as eluent, the main fractions were recrystallized from CH₂Cl₂/cyclohexane to afford pure 17.5g of **268a**.

10

¹H NMR (CDCl₃) δ 7.79 (t, J = 4.0 Hz, 1H), 7.65 (t, J = 7.9Hz, 1H), 7.58 (m, 1H), 7.70-7.35 (t, J = 8.1 Hz, 1H), 7.06 (m, 2H), 5.07 (d, J = 3.8 Hz, 2H), 3.88 (s, 3H).



N-[(5-{[4-(2,4-difluorobenzoyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide, 268

268 was prepared using the general procedure protocol applied for the preparation of 2
5 and could be isolated as colorless solid in 98% yield (62mg).). M/Z APCI : 535 (M+1),
533 (M-1). Anal. HPLC: rt. = 6.22 min (method a).

Example 269: Preparation of 2-Hydroxy-N-({5-[(4-{3-[(trifluoromethyl)sulfonyl]-anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide 269

10 Diallyl-thiophen-2-ylmethylamine 269a

A solution of 2-aminomethyl-thiophene (51.4 g, 956 mmol) and *i*-Pr₂NEt (140 g, 1081 mmol) in CH₂Cl₂ (1 l) was placed in a 3-l flask equipped with a condenser and an efficient magnetic agitation. Allyl bromide (115.7 g, 454 mmol) was added, whereupon the moderately exothermic reaction spontaneously reached the reflux temperature after 2 h.
15 The mixture was stirred overnight (16 h), washed (NaHCO₃ sat.; brine), dried (MgSO₄), and concentrated. The resulting oil was filtered over silica gel (EtOAc:hexane 1:4). The filtrate was concentrated and the filtration was repeated to afford 70.3 g (80%) of the title diallylamine as a brown-yellow oil, clean by NMR: ¹H NMR (CDCl₃) δ 7.25 (br. d, *J* = 5.9 Hz, 1H), 6.98 (br. dd, *J* = 5.1, 2.8 Hz, 1H), 6.94–6.92 (m, 1H), 5.99–5.86 (m, 2H), 5.29–5.18 (m, 4H), 3.85 (s, 2H), 3.16 (dd, *J* = 6.3, 0.9 Hz, 4H).
20

5-Diallylaminomethyl-thiophene-2-sulfonyl chloride 269b

A solution of the allyl-protected thiophene 269a (6.2 g, 32.1 mmol) in Et₂O was cooled
25 to –70°C by means of an acetone/dry ice bath. A solution of *t*-BuLi in pentane (21.38 mL, 1.5M, 32.1 mmol) was added over 2 min whereupon the internal temperature momentarily rose to –50°C and the mixture turned orange. After 10 min., SO₂ was bubbled for 2 min, which led to the immediate formation of a thick precipitate. The reaction was allowed to reach 0°C, and a suspension of NCS (4.63 g, 32.1 mmol) in THF (20 mL)
30 was added, whereupon the slurry turned purple. After 45 min at r.t., the mixture was filtered over SiO₂, eluting with EtOAc. Evaporation, dilution with EtOAc:hexane 1:5



and filtration over SiO₂ gave 5.0 g (53%) of the title sulfonyl chloride **269b** as a pale brown oil which was used without further purification.

N,N-Diallyl-*N*-(5-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]-thien-2-yl)methyl)amine **269c**

A solution of 4-(3-trifluoromethanesulfonyl-phenylamino)-piperidine (731 mg, 2.37 mmol) and Et₃N (0.5 mL, 3.58 mmol) in CH₂Cl₂ (20 mL) was treated with the diallylamino sulfonyl chloride **269b** 23°C. A thick precipitate appeared within 5 min, and the mixture was stirred overnight (even if complete within minutes). Dilution with CH₂Cl₂ (50 mL), washing (H₂O; brine), drying (MgSO₄), and evaporation afforded the crude product, which was filtered over silica gel (AcOEt:cyclohexane 1:1) to afford 1.15 g (86%) of the title bisallylamine, which was used in the next step without further purification.

2-Hydroxy-*N*-(5-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]-thien-2-yl)methyl)benzamide **269**

A solution of the bisallylamine **269c** (1.15 g, 2.04 mmol), *N,N'*-dimethylbarbituric acid (NDMBA, 637 mg, 4.08 mmol), and Pd(PPh₃)₄ (110 mg, 0.096 mmol) in CH₂Cl₂ (20 mL) was degassed by bubbling argon for 10 min. The reaction was stirred at 23°C over the week-end (3 d), concentrated, diluted with DMF (12 mL), and treated with salicylic acid (290 mg, 2.10 mmol), 1-hydroxybenzotriazole (HOBt, 283 mg, 2.10 mmol), and *N*-ethyl-*N'*-(3-dimethylaminopropyl)-carbodiimide (EDC, 402 mg, 2.10 mmol) for 24 h at 23°C. Dilution with EtOAc, washing (H₂O, NaHCO₃ sat., brine), drying (MgSO₄), and evaporation afforded the crude 3-hydroxybenzamide. Purification by reverse-phase prep. HPLC (C8, H₂O:CH₃CN 60:40 → 0:100 over 40 min, r.t. = 23 min) and freeze-drying afforded 466 mg (38% from **269c**) of the title 3-hydroxybenzamide as a white powder: ¹H NMR (DMSO-*d*₆) δ 12.1 (s, 1H), 9.48 (t, *J* = 5.9 Hz, 1H), 7.86 (dd, 7.9, 1.5 Hz, 1H), 7.50 (d, *J* = 3.8 Hz, 1H), 7.45 (t, *J* = 8.1 Hz, 1H), 7.41 (dd, *J* = 8.9, 1.5 Hz, 1H), 7.21 (d, *J* = 3.8 Hz, 1H), 7.18–7.10 (m, 3H), 6.93 (d, *J* = 8.3 Hz, 1H), 6.91 (td, *J* = 8.4, 1.1 Hz, 1H), 6.52 (d, *J* = 7.7 Hz, 1H), 4.73 (d, *J* = 5.8 Hz, 2H), 3.57–3.47 (br. d, *J* = 12.1, 2H), 3.52–3.35 (br. m., 1H), 2.62 (t, *J* = 10.4 Hz, 2H), 2.07 (s, 1.2H, residual CH₃CN), 2.02–1.92 (br. d, *J* = 10.4 Hz, 2H), 1.47 (qd, *J* ≈ 11.2, 3.6 Hz, 2H). ¹³C NMR (DMSO-*d*₆) δ 167.52 (s, C=O), 158.36 (s), 148.98 (s), 147.85 (s), 132.83 (d), 132.74 (s),



131.47 (d), 130.00 (d), 128.98 (s), 127.09 (d), 125.52 (d), 124.83 (s), 118.92 (q, residual CH₃CN), 118.34 (q, $J = 326$ Hz, CF₃), 117.75 (d), 116.24 (d), 115.23 (d), 114.19 (q), 111.33 (d), 45.93 (d), 43.66 (t), 36.66 (t), 29.18 (t), 0.00 (s, residual CH₃CN). M/Z APCI : 604 (M+1), 602 (M-1). Anal. HPLC: R.t = 6.60 min (method a).

- 5 C₂₄H₂₄F₃N₃O₆S₃ · 0.3 CH₃CN · 1.0 H₂O Calc.: C: 47.53%. H: 4.36%. N: 7.44%. Found: C: 47.41%, H: 4.09%, N: 7.49%.

In this protocol, salicylic acid could be replaced with other carboxylic acids, which include (but are not limited to): 4-chlorobenzoic acid, 4-nitrobenzoic acid, 3-nitrobenzoic acid, 3-methoxybenzoic acid, 5-nitro-1H-pyrazole-3-carboxylic acid, 2-hydroxynicotinic acid, 2-mercaptopyridine-3-carboxylic acid, 3,4-dihydroxybenzoic acid, 2-picolinic acid.

The following compounds were prepared on a parallel fashion according to the examples described above

The following table provides HPLC data and mass spectroscopy data of the mentioned examples

Exemple	Name	Rt HPLC	Purity	Gradient HPLC	Mass M+1	Mass M
270	N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide	5.55	91.6	a	512	510
271	N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-2-hydroxybenzamide	5.6	89.4	a	498	496
272	N-[(5-{[4-(1,3-dithiolan-2-yl)anilino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide	5.74	88.1	a	605	603
273	3-methoxy-N-[(5-{[4-(3-methoxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	4.58	88.6	a	516	514
274	3-methoxy-N-[(5-{[4-[3-(trifluoromethyl)anilino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide	6.5	97.5	a	554	552
275	N-[(5-{[4-[3-(dimethylamino)anilino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide	4.4	83.1	a	530	528
276	3-methoxy-N-[(5-{[4-(3-propylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide	5.29	93.3	a	528	526
277	3-methoxy-N-[(5-{[4-[3-(methylsulfonyl)anilino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide	5.59	95.7	a	564	562
278	3-methoxy-N-[(5-{[4-[3-(methylsulfonyl)anilino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-benzamide	5.5	97	a	532	530

279	N-{{5-({4-[3-(aminosulfonyl)anilino]piperidin-1-yl)sulfonyl}thien-2-yl)methyl}-3-methoxybenzamide	5.2	93.8	a	565	563
280	methyl 3-({1-[(5-{{3-methoxybenzoyl}amino}-methyl)thien-2-yl)sulfonyl]piperidin-4-yl}amino)-benzoate	5.76	96.8	a	544	542
281	N-{{5-({4-[3-(aminocarbonyl)anilino]piperidin-1-yl)sulfonyl}thien-2-yl)methyl}-3-methoxybenzamide	4.08	95.4	a	529	527
282	3-methoxy-N-[(5-{{4-(2-methoxyanilino)piperidin-1-yl)sulfonyl}thien-2-yl)methyl]benzamide	4.58	90.2	a	516	514
283	N-({5-[(4-{3-nitroanilino}piperidin-1-yl)sulfonyl]thien-2-yl)methyl}-3-methoxybenzamide	6.44	89.3	a	531	529
284	3-methoxy-N-{{5-({4-[2-(trifluoromethyl)anilino]piperidin-1-yl)sulfonyl}thien-2-yl)methyl}-benzamide	7.15	96.9	a	554	552
285	N-({5-[(4-{2-nitroanilino}piperidin-1-yl)sulfonyl]thien-2-yl)methyl}-3-methoxybenzamide	6.59	95.2	a	531	529
286	N-{{5-({4-[4-(aminocarbonyl)anilino]piperidin-1-yl)sulfonyl}thien-2-yl)methyl}-3-methoxybenzamide	4.57	95.2	a	529	0
287	N-{{5-({4-[4-(1,3-dithiolan-2-yl)anilino]piperidin-1-yl)sulfonyl}thien-2-yl)methyl}-3-methoxybenzamide	5.64	96.6	a	599	597
288	N-[(5-{{4-(3-chloroanilino)piperidin-1-yl)sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide	6.57	97.7	a	520	518
289	N-[(5-{{4-(4-chloroanilino)piperidin-1-yl)sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide	6.86	100	a	520	518
290	3-methoxy-N-({5-[(4-{4-(trifluoromethyl)sulfonyl}anilino)piperidin-1-yl)sulfonyl]thien-2-yl)methyl}benzamide	6.88	98	a	618	616
291	N-({5-[(4-{3-[amino(imino)methyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl)methyl}-3-methoxybenzamide	4.18	91.3	a	528	526
292	N-({5-[(4-{3-[(2-hydroxyethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl)methyl}-3-methoxybenzamide	5.11	92.2	a	594	592
293	3-methoxy-N-({5-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl)methyl}-benzamide	6.55	88.1	a	618	616
294	N-({5-[(4-anilinopiperidin-1-yl)sulfonyl]thien-2-yl)methyl}-3-methoxybenzamide	4.52	88.5	a	486	484
295	3-methoxy-N-({5-[(4-{3-[(trifluoromethyl)sulfanyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl)methyl}-benzamide	6.54	92.9	a	586	584
296	N-[(5-{{4-(4-hydroxyanilino)piperidin-1-yl)sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide	3.98	88	a	502	500
297	3-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfanyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl)methyl}-benzamide	7.23	88	a	601	599
298	4-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfanyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl)methyl}-benzamide	7.28	90.4	a	601	599
299	N-[(5-{{4-(2-hydroxyanilino)piperidin-1-yl)sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide	4.12	89.8	a	502	500
300	3-methoxy-N-[(5-{{4-(pyrimidin-2-ylamino)-	4.15	92.7	a	488	486

	piperidin-1-yl)sulfonyl} thien-2-yl)methyl]-benzamide					
301	N-{{5-({4-[(3-aminopyridin-2-yl)amino]piperidin-1-yl)sulfonyl}thien-2-yl)methyl}-3-methoxybenzamide	3.96	93.1	a	502	500
302	N-[(5-{{4-[(3-nitropyridin-2-yl)amino]piperidin-1-yl)sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide	6.22	100	a	532	530
303	N-{{5-({4-[(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)amino]piperidin-1-yl)sulfonyl}thien-2-yl)methyl}-3-methoxybenzamide	5.04	98.5	a	576	574
304	N-[(5-{{4-[(2,3-dihydro-1H-inden-5-ylamino)-piperidin-1-yl)sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide	4.81	97.1	a	526	524
305	3-methoxy-N-[(5-{{4-(2-propylanilino)piperidin-1-yl)sulfonyl}thien-2-yl)methyl]benzamide	5.99	99	a	528	526
306	3-methoxy-N-[(5-{{4-(4-propylanilino)piperidin-1-yl)sulfonyl}thien-2-yl)methyl]benzamide	5.15	97.9	a	528	526
307	N-[(5-{{4-(3-tert-butylanilino)piperidin-1-yl)sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide	5.41	98.9	a	542	540
308	N-({5-{{4-[(3-chloro-5-(trifluoromethyl)pyridin-2-yl)amino]piperidin-1-yl)sulfonyl}thien-2-yl)methyl)-3-methoxybenzamide	7.23	96.1	a	589	587
309	3-methoxy-N-[[5-({4-[3-(1,3-oxazol-5-yl)anilino]-piperidin-1-yl)sulfonyl}thien-2-yl)methyl]-benzamide	5.25	94.9	a	553	551
310	N-[(5-{{4-([1,1'-biphenyl]-3-ylamino)piperidin-1-yl)sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide	5.82	97.1	a	562	560
311	3-methoxy-N-[(5-{{4-(3-propylphenoxy)piperidin-1-yl)sulfonyl}thien-2-yl)methyl]benzamide	7.55	78.7	a	529	527
312	3-methoxy-N-{{5-({4-[3-(morpholin-4-yl)sulfonyl]-anilino]piperidin-1-yl)sulfonyl}thien-2-yl)methyl}-benzamide	5.85	96.9	a	635	633
313	3-methoxy-N-[(5-{{4-(2-phenylethyl)piperidin-1-yl)sulfonyl}thien-2-yl)methyl]benzamide	7.2	98.3	a	499	497
314	N-[(5-{{4-(3-benzylanilino)piperidin-1-yl)sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide	5.77	97.6	a	576	574
315	3-methoxy-N-[(5-{{4-(3-phenylpropyl)piperazin-1-yl)sulfonyl}thien-2-yl)methyl]benzamide	4.33	99.7	a	514	512
316	3-methoxy-N-({5-{{4-[(4-(trifluoromethyl)-pyrimidin-2-yl)amino]piperidin-1-yl)sulfonyl}thien-2-yl)methyl}benzamide	5.69	100	a	556	554
317	N-[(5-{{4-(3-cyclohexyl-4-hydroxyanilino)-piperidin-1-yl)sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide	4.76	91.7	a	584	582
318	N-({5-{{4-[(3-(butylamino)sulfonyl]anilino)-piperidin-1-yl)sulfonyl}thien-2-yl)methyl}-3-methoxybenzamide	5.77	99.3	a	621	619
319	N-[(5-{{4-(3-ethyl-anilino)piperidin-1-yl)sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide	4.54	94.4	a	514	512
320	3-methoxy-N-[(5-{{4-(5,6,7,8-tetrahydronaphthalen-1-ylamino)piperidin-1-yl)sulfonyl}thien-2-yl)methyl]benzamide	5.02	88.2	a	540	538
321	N-[(5-{{4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl)sulfonyl}thien-2-yl)methyl]-5-nitro-1H-pyrazole-3-carboxamide	5.12	96.2	a	517	515
322	N-[(5-{{4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-	4.15	93	a	499	497

	yl)sulfonyl} thien-2-yl)methyl]-2-oxo-1,2-dihydropyridine-3-carboxamide					
323	N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl)sulfonyl} thien-2-yl)methyl]-2-thioxo-1,2-dihydropyridine-3-carboxamide	4.43	85.8	a	515	513
324	N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl)sulfonyl} thien-2-yl)methyl]-3,4-dihydroxybenzamide	4.62	89.1	a	514	512
325	N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl)sulfonyl} thien-2-yl)methyl]pyridine-2-carboxamide	5.22	98.9	a	483	481

Example 326: Preparation of N-[(5-{[4-(hexyloxy)piperidin-1-yl)sulfonyl} thien-2-yl)methyl]-3-methoxybenzamide 326

5 **N,N-diallyl-N-[(5-{[4-(hexyloxy)piperidin-1-yl)sulfonyl} thien-2-yl)methyl]amine 326a**

To a solution of 4-hydroxy-piperidine (190mg, 1.88 mmol) and DIEA (0.87mL, 5.13 mmol) in 10 mL CH₂Cl₂ was added a solution of 5-([1-(4-Chloro-phenyl)-methanoyl]-amino)-methyl)-thiophene-2-sulfonyl chloride 1b (500mg, 1.71mmol) in hot DCE. The reaction mixture was stirred for 4h. 100mL EtOAc were added and excess of amines were removed by extraction with HCl (1N). The sulfonamide intermediate was used without any further purification, where 300mg (0.84mmol) were dissolved in dry DMF under Ar. NaH (60mg, 50% in parafine oil, 1.01mmol) were added as a solid. The colour of the reaction changed to orange. The reaction mixture was stirred for 15' until no gas evolution was observed anymore. Iodohexane (356mg, 1.68mmol) dissolved in 1mL DMF was added to the above solution and the reaction mixture was heated at 70°C overnight. DMF was evaporated to dryness and the crude was taken up in CH₂Cl₂. The organic layer was washed twice with water, dried over MgSO₄ and evaporated to dryness. The crude was purified on silica gel using cyclohexane/EtOAc 3:1 as eluent to obtain 210 mg (59%) of pure **326a** as a colorless oil.

20 **N-[(5-{[4-(hexyloxy)piperidin-1-yl)sulfonyl} thien-2-yl)methyl]-3-methoxybenzamide 326**

A solution of **326a** (134mg, 0.3mmol), 1,3 Dimethylbarbituric acid (94mg, 0.6mmol) and Tetrakis(triphenylphosphine)palladium (12mg, 0.01mmol) were stirred under Argon in 3 mL CH₂Cl₂. The reaction was followed by HPLC until all starting material disappeared. The crude was evaporated to dryness and taken up in dry THF. To this solu-



tion was added DIEA (230ul, 1.5mmol) and 3-anisoylchloride (51mg, 0.3mmol). The reaction was stirred for 3h, EtOAc was added and the organic layer was extracted with NaHCO₃ sat., HCl (0.1N) and brine. The dry solution was evaporated and purified by flash chromatography on silica gel using cyclohexane/EtOAc 7:3 as eluent. **326** was obtained as an oil (54mg, 37%): ¹H NMR (CDCl₃) δ 7.43-7.25 (m, 4H), 7.15-7.05 (m, 2H), 6.60 (m, 1H), 4.83 (d, *J* = 6.0 Hz, 2H), 3.86 (s, 3H), 3.35 (d, *J* = 6.6, 2H), 3.35-3.23 (m, 3H), 2.95 (m, 2H), 1.94 (m, 2H), 1.86 (m, 2H), 1.70-1.50 (m, 5H), 1.30-1.20 (m, 8H), 0.87 (t, *J* = 6.8, 3H), M/Z APCI: 495.2 (M+1).

Example 327: Preparation of *N*-({5-[(4-heptanoylpiperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide **327**

Methyl 1-({5-[(diallylamino)methyl]thien-2-yl}sulfonyl)piperidine-4-carboxylate **327a**

5-Diallylaminomethyl-thiophene-2-sulfonyl chloride **229b** (270 mg, 1.88mmol) and DIEA (0.88mL, 5.13mmol) were dissolved in 10 mL chloroform. This solution was added methylisonipecotate (269 mg, 1.88mmol) in 1 mL chloroform. The reaction was stirred for 3h, diluted with CH₂Cl₂ and extracted with HCl (0.1N), NaHCO₃ sat. and brine. The organic layer was dried over MgSO₄ and evaporated to dryness. The crude was purified by flash chromatography on silica gel using cyclohexane/EtOAc 1:1 as eluent to obtain 440 mg (65%) of **327a** as colorless oil: ¹H NMR (CDCl₃) δ 7.30 (d, *J* = 3.6 Hz, 1H), 6.83 (d, *J* = 3.6 1H), 5.78 (m, 2H), 5.18 (m, 4H), 3.70 (s, 2H), 3.52 (m, 6H), 3.07 (m, 4H), 2.50 (m, 2H), 2.25 (m, 1H), 1.93 (m, 2H), 1.84 (m, 2H). M/Z APCI: 399.2 (M+1)

1-({5-[(diallylamino)methyl]thien-2-yl}sulfonyl)-*N*-methoxy-*N*-methylpiperidine-4-carboxamide **327b**

327a (390mg, 1mmol) and *N,O*-dimethylhydroxylamine (148mg, 1.52mmol) were stirred at -20°C in anhydrous THF, while Isopropylmagnesium chloride in THF (2M, 1.65mL, 3.23mmol) were slowly added. The reaction mixture was allowed to warm to r.t. during 30', followed by an additional stirring at r.t. for 30'. The reaction is quenched



with ammoniumchloride solution (20%). The aqueous layer is extracted with t-butylmethylether, and the combined organic layers are washed with brine, dried over MgSO₄ and evaporated to dryness. The crude is purified by flash chromatography on silica gel using cyclohexan/EtOAc 1:1 as eluent. **327b** (380 mg, 90%) was obtained as a colourless solid: H¹ NMR (DMSO *d*6) δ 7.53 (d, *J* = 3.7 Hz, 1H), 7.16 (d, *J* = 3.6 1H), 5.89 (m, 2H), 5.24 (m, 4H), 3.86 (s, 2H), 3.62 (m, 5H), 3.15 (m, 7H), 2.74 (m, 1H), 2.50 (m, 2H), 2.25 (m, 2H), 1.84 (m, 2H), 1.63 (m, 2H). M/Z APCI: 428.1 (M+1).

1-[1-({5-[(diallylamino)methyl]thien-2-yl}sulfonyl)piperidin-4-yl]heptan-1-one **327c**

327b (376mg, 0.88mmol) was dissolved in anhydrous THF and cooled to -20 °C. To this solution was added dropwise at -20°C hexyllithium (2M in hexane) (2.46mL, 6.2 mmol). The reaction was allowed to warm to rt. during 3h and poured on 100mL HCl /EtOH (5%). The aqueous phase was extracted with CH₂Cl₂ and the combined organic layers are washed with NaOH (2N) and brine, dried over MgSO₄ and evaporated to dryness. The crude material was purified by flash chromatography on silica gel using cyclohexane/EtOAc 4:1 as eluent to obtain 186 mg (47%) of (**327c**) as a brownish oil: H¹ NMR (CDCl₃) δ 7.40 (d, *J* = 3.6 Hz, 1H), 7.25 (d, *J* = 3.6 1H), 5.95 (m, 2H), 5.50 (m, 4H), 4.32 (s, 2H), 3.70-3.50 (m, 6H), 2.50 (m, 2H), 2.32 (m, 3H), 1.85 (m, 2H), 1.68 (m, 2H), 1.46 (m, 2H), 1.30-1.12 (m, 6H), 0.80 (t, *J* = 6.6 Hz, 3H), M/Z APCI: 453.2 (M+1)

N-({5-[(4-heptanoylpiperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide **327**

A solution of **327c** (100mg, 0.22mmol), 1,3Dimethylbarbituric acid (69mg, 0.44mmol) and Tetrakis(triphenylphosphine)palladium (12 mg, 0.01mmol) were stirred in 3 mL CH₂Cl₂ overnight. The deprotection was followed by TLC. After complete cleavage of the protecting groups, the solvent was evaporated to dryness. The crude was taken up in THF, DIEA (76ul, 0.33mmol) was added, followed by the slow addition of 3-anisoylchloride (38mg, 0.22mmol) in THF. The reaction was stirred for 3h, diluted with EtOAc and extracted with NaHCO₃ and brine. The organic layers were dried over Na₂SO₄ and evaporated to dryness. The crude mixture was purified by flash chroma-



tography on silica gel using cyclohexane/EtOAc 1:1 as eluent to obtain 30mg (50%) of **327** as a colorless oil: ^1H NMR (CDCl_3) δ 7.40-7.10 (m, 3H), 6.95 (m, 2H), 6.45 (m, 1H), 4.70 (d, $J = 6.0$ Hz, 2H), 3.74 (s, 3H), 3.58 (m, 2H), 2.40 (m, 2H), 2.27 (t, $J = 7.5$ Hz, 2H), 2.19 (m, 1H), 1.77 (m, 2H), 1.64 (m, 2H), 1.13 (m, 8H), 0.74 (t, $J = 6.8$ Hz, 3H), M/Z APCI: 506.3 (M+1).

Example 328: Preparation of 4-chloro-N-[(5-{[4-(3-propylanilino)piperidin-1-yl]sulfonyl}-2-furyl)methyl]benzamide 328

4-Chloro-N-2-furylmethyl-benzamide 328a

A solution of 4-chlorobenzoyl chloride (3.2g, 18.5 mol) in 50 ml dry CH_2Cl_2 was added over 30 min to a stirred solution of 2-furfurylamine (2g, 20.6 mol) and $^i\text{Pr}_2\text{NEt}$ (7ml, 41 mol) in CH_2Cl_2 (200 ml) at 0°C . The reaction was allowed to warm to room temperature over 3 h. The mixture was diluted with 200 ml of CH_2Cl_2 , washed twice with HCl aq. (1N) and dried over MgSO_4 . Evaporation of the solvent afforded 4g (83%) of the title benzamide as a white solid: ^1H NMR ($\text{DMSO}-d_6$) δ 9.05 (t, $J = 5.7$ Hz, 1H), 7.89 (d, $J = 8.7$ Hz, 2H), 7.57 (m, 1H), 7.53 (d, $J = 8.7$ Hz, 2H), 6.40 (dd, $J = 3.7, 1.1$ Hz, 1H), 6.28 (d, $J = 3.7$ Hz, 1H), 4.46 (d, $J = 5.6$ Hz, 2H). M/Z APCI : 236.6 (M+1), 234.8 (M-1).

5-({[1-(4-Chloro-phenyl)-methanoyl]-amino}-methyl)-furane-2-sulfonyl chloride 328b

Chlorosulfonic acid (494mg, 4.24 mmol) in CH_2Cl_2 (10 ml) was added dropwise to a solution of **9a** (500mg, 2.12 mmol) in CH_2Cl_2 (20 ml) at -80°C . The mixture was allowed to reach room temperature in 5h. Excess of sulfonic acid was quenched with ice and NaHCO_3 . 1.62 ml (40% aqueous sol., 2.54 mmol) of Tetrabutylammonium hydroxide were added, and the so formed salt was extracted with DCM. The organic layer was dried over MgSO_4 , filtered and evaporated to dryness. A red coloured oil (1.11g) could isolated in 94% yield, which was used for the following step with any further purification.

The intermediate sulfonic acid tetrabutylammonium salt (1.1g, 1.97 mmol) was dissolved in 20ml DCM and flushed with Argon. Triphosgene (410mg, 1.38 mmol) was



added as a solid followed by the addition of a solution of 60 μ l DMF in 2ml DCM. The reaction was stirred under Ar. for 3h at r.t. The solvent was evaporated using reduced pressure, and the crude oily residue was purified by flash chromatography using PE/EtOAc 2:1 as eluant. Main fractions afforded 450mg (69%) of title sulfonylchloride

5 **328b**. ^1H NMR (CDCl_3) δ 7.57 (d, J = 8.7 Hz, 2H), 7.27 (d, J = 8.7 Hz, 2H), 7.09 (d, J = 3.4 Hz, 1H), 6.43 (t, b, 1H), 6.40 (d, J = 3.4 Hz, 1H), 4.57 (d, J = 6.0 Hz, 2H).

4-chloro-N-[(5-{[4-(3-propylanilino)piperidin-1-yl]sulfonyl}-2-furyl)methyl]benzamide
328

- 10 **328** was synthesised according to the protocol for the synthesis of **2**. Isolated yield: 21 mg (82%). Anal. HPLC: R.t = 5.34 min (method a). M/Z APCI: 516.2 (M+1), 514.1 (M-1).

The following compounds were prepared on a parallel fashion according to the examples described above

15

The following table provides HPLC data and mass spectroscopy data of the mentioned examples

Exemple	Name	rt HPLC	Purity	Gradient HPLC	Mass M+1	Mass M
329	4-chloro-N-[(5-{[4-(3-chloroanilino)piperidin-1-yl]sulfonyl}-2-furyl)methyl]benzamide	6.41	97.8	a	508	506
330	4-chloro-N-[(5-{[4-(3-methoxyanilino)piperidin-1-yl]sulfonyl}-2-furyl)methyl]benzamide	4.86	92	a	504	502
331	4-chloro-N-[(5-{[4-(3-(trifluoromethyl)anilino)piperidin-1-yl]sulfonyl}-2-furyl)methyl]benzamide	6.73	96.8	a	542	540
332	4-chloro-N-[(5-{[4-(3-(dimethylamino)anilino)piperidin-1-yl]sulfonyl}-2-furyl)methyl]benzamide	4.29	93.6	a	517	515
333	4-chloro-N-[(5-{[4-(3-(methylsulfonyl)anilino)piperidin-1-yl]sulfonyl}-2-furyl)methyl]benzamide	5.42	98	a	552	550
334	4-chloro-N-[(5-{[4-(3-(methylsulfonyl)anilino)piperidin-1-yl]sulfonyl}-2-furyl)methyl]benzamide	5.46	96	a	520	518
335	N-[(5-{[4-(3-(aminosulfonyl)anilino)piperidin-1-yl]sulfonyl}-2-furyl)methyl]-4-chlorobenzamide	5.08	94	a	553	551
336	methyl 3-({1-[(5-{[4-(4-chlorobenzoyl)amino]methyl}-2-furyl)sulfonyl]piperidin-4-yl}amino)-benzoate	5.64	98	a	532	530
337	3-({1-[(5-{[4-(4-chlorobenzoyl)amino]methyl}-2-furyl)sulfonyl]piperidin-4-yl}amino)benzamide	4.3	97.1	a	517	515
338	4-chloro-N-[(5-{[4-(3-nitroanilino)piperidin-1-	6.22	87.4	a	519	517

	yl)sulfonyl]-2-furyl)methyl)benzamide					
339	4-chloro-N-[(5-[(4-(2-methoxyanilino)piperidin-1-yl)sulfonyl]-2-furyl)methyl]benzamide	4.56	98.4	a	504	502
340	4-chloro-N-[(5-[(4-(2-(trifluoromethyl)anilino)piperidin-1-yl)sulfonyl]-2-furyl)methyl]benzamide	6.86	97.6	a	542	540
341	4-chloro-N-[(5-[(4-(2-nitroanilino)piperidin-1-yl)sulfonyl]-2-furyl)methyl]benzamide	6.29	97.9	a	519	517
342	4-chloro-N-[(5-[(4-(4-chloroanilino)piperidin-1-yl)sulfonyl]-2-furyl)methyl]benzamide	5.88	98.1		508	506
343	4-chloro-N-[(5-[(4-(4-(trifluoromethyl)anilino)piperidin-1-yl)sulfonyl]-2-furyl)methyl]benzamide	6.73	96.9		542	540
344	4-chloro-N-[(5-[(4-(4-(trifluoromethyl)sulfonyl)anilino)piperidin-1-yl)sulfonyl]-2-furyl)methyl]benzamide	6.57	99.1		606	604
345	N-[(5-[(4-(4-(aminocarbonyl)anilino)piperidin-1-yl)sulfonyl]-2-furyl)methyl]-4-chlorobenzamide	4.61	94.3		517	515
346	4-chloro-N-[(5-[(4-(4-(1,3-dithiolan-2-yl)anilino)piperidin-1-yl)sulfonyl]-2-furyl)methyl]benzamide	5.55	96.7		578	576
347	N-[(5-[(4-(3-[amino(imino)methyl]anilino)piperidin-1-yl)sulfonyl]-2-furyl)methyl]-4-chlorobenzamide	4.07	94.5		516	514
348	4-chloro-N-[(5-[(4-(3-[(trifluoromethyl)sulfonyl]anilino)piperidin-1-yl)sulfonyl]-2-furyl)methyl]benzamide	6.77	94.7	a	606	604
349	N-[(5-[(4-anilinopiperidin-1-yl)sulfonyl]-2-furyl)methyl]-4-chlorobenzamide	4.52	93.8		474	472
350	4-nitro-N-[(5-[(4-(3-[(trifluoromethyl)sulfonyl]anilino)piperidin-1-yl)sulfonyl]-2-furyl)methyl]benzamide	7.12	97	a	574	572

Example 351 Preparation of 4-chloro-N-[(5-[(3-[(trifluoromethyl)sulfonyl]anilino)pyrrolidin-1-yl)sulfonyl]thien-2-yl)methyl]benzamide 351

5 **4-chloro-N-[(5-[(3R)-3-hydroxypyrrolidin-1-yl)sulfonyl]thien-2-yl)methyl]benzamide 351a**

To a suspension of R-3-pyrrolidinol hydrochloride (530mg, 4.29 mmol) and DIEA (0.75ml, 14.3mmol) in CH₂Cl₂/DMF 1:1 was added a solution of 5-([1-(4-Chlorophenyl)-methanoyl]-amino)-methyl)-thiophene-2-sulfonyl chloride 1b (1.0g, 2.86mmol). At the end of addition the suspension disappeared. The reaction mixture was stirred overnight. 100ml EtOAc were added and the excess of amine was extracted with HCl (1N), followed by washings with brine. The organic layers were dried over MgSO₄ and evaporated to dryness to provide 351a (1.14 g, 99.9%) as a colourless foam: H¹ NMR (DMSO d₆) δ 9.34 (t, J = 5.8 Hz, 1H), 7.89 (d, J = 8.7 Hz, 2H), 7.49 (d, J = 3.8 Hz, 1H), 7.55 (d, J = 8.7 Hz, 2H), 7.13 (d, J = 3.8 Hz, 1H), 4.95 (d, J = 3.4 Hz, 1H),

4.65 (d, $J = 5.6$ Hz, 2H), 4.16 (m, 1H), 3.40-3.20 (m, 5H), 3.00 (m, 1H), 3.35-3.23 (m, 3H), 1.80-1.60 (m, 2H), M/Z APCI: 401.2 (M+1), 398.9 (M-1).

4-chloro-*N*-({5-[(3-oxopyrrolidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide 351b

5 At -80°C oxalylchloride (36mg, 0.28mmol) was dissolved in dry CH_2Cl_2 , while DMSO (50ul, 0.6 mmol) were added slowly. The solution was stirred under Ar. For 15'. **351a** (100mg, 0.25mmol) was dissolved in 2ml CH_2Cl_2 , and this solution was added dropwise to the above reaction mixture at -80°C . The reaction was stirred for 15' at low temperature, before DIEA (0.21ml, 1.25mmol) was added. The reaction was stirred at –
10 80°C for 30' and allowed to warm to rt. during 2h. A white solid was formed, the reaction was quenched with water and extracted with CH_2Cl_2 several times. The combined organic layers were dried over MgSO_4 and evaporated to dryness. The crude was purified by flash chromatography on silica gel using EtOAc/cyclohexane 2:1 as eluent. **351b** (80mg, 80%) was obtained as a colourless solid.: ^1H NMR (CDCl_3) δ 7.72
15 (d, $J = 8.7$ Hz, 2H), 7.46 (d, $J = 3.8$ Hz, 1H), 7.42 (d, $J = 8.7$ Hz, 2H), 7.08 (d, $J = 3.8$ Hz, 1H), 6.59 (t, $J = 5.8$, 1H), 4.80 (d, $J = 6.0$ Hz, 2H), 3.58 (t, $J = 7.5$ Hz, 2H), 3.50 (s, 3H), 2.54 (t, $J = 7.5$, 2H), 3.35-3.23 (m, 3H), 2.95 (m, 2H), 1.94 (m, 2H), 1.86 (m, 2H), 1.70-1.50 (m, 5H), 1.30-1.20 (m, 8H), 0.87 (t, $J = 6.8$, 3H), M/Z APCI 399.0 (M+1), 397.2 (M-1)

20 4-chloro-*N*-({5-[(3-{3-[(trifluoromethyl)sulfonyl]anilino}pyrrolidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide 351
351b was prepared according to the protocol #1 example 110 and was isolated as colourless solid in 84% yield (15mg). M/Z APCI: 609 (M+1), 607 (M-1).)

25 **Example 352 :Preparation of 4-chloro-*N*-({5-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}-azepan-1-yl)sulfonyl]thien-2-yl}methyl)benzamide 352**

352 was prepared according to the protocol #1 example 110 and was isolated as colourless solid in 47% yield (12mg). M/Z APCI: 637 (M+1), 639 (M-1).).
30

Example 353 : Preparation of a pharmaceutical formulation

The following formulation examples illustrate representative pharmaceutical compositions according to the present invention being not restricted thereto.

Formulation 1 – Tablets

- 5 A sulfonamide compound of formula I is admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate is added as a lubricant. The mixture is formed into 240-270 mg tablets (80-90 mg of active sulfonamide compound per tablet) in a tablet press.

10 **Formulation 2 – Capsules**

A sulfonamide compound of formula I is admixed as a dry powder with a starch diluent in an approximate 1:1 weight ratio. The mixture is filled into 250 mg capsules (125 mg of active sulfonamide compound per capsule).

Formulation 3 – Liquid

- 15 A sulfonamide compound of formula I (1250 mg), sucrose (1.75 g) and xanthan gum (4 mg) are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously prepared solution of microcrystalline cellulose and sodium carboxymethyl cellulose (11:89, 50 mg) in water. Sodium benzoate (10 mg), flavor, and color are diluted with water and added with stirring. Sufficient water is then added to produce a total
20 volume of 5 mL.

Formulation 4 – Tablets

- A sulfonamide compound of formula I is admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate is added as a lubricant. The mixture is formed into 450-900 mg tablets (150-300 mg of
25 active sulfonamide compound) in a tablet press.

Formulation 5 – Injection

A sulfonamide compound of formula I is dissolved in a buffered sterile saline injectable aqueous medium to a concentration of approximately 5 mg/mL.

Example 354: Biological assays**Biological Results**

The activities of the sulfonamide derivatives claimed in the formula I were assessed using the above described *in vitro* and *in vivo* biological assays.

JNK 2 and 3 in vitro assays: JNK3 and/or 2 assays are performed in 96 well MTT plates, by incubation of 0.5 µg of recombinant, pre-activated GST-JNK3 or GST-JNK2 with 1 µg of recombinant, biotinylated GST-c-Jun and 2 µM ³³γ-ATP (2 nCi/µl), in the presence or absence of sulfonamide inhibitors if formula I and in a reaction volume of 50 µl containing 50 mM Tris-HCl, pH 8.0; 10 mM MgCl₂; 1 mM Dithiothreitol, and 100 µM NaVO₄. The incubation is performed for 120 min. at R.T and stopped upon addition of 200 µl of a solution containing 250 µg of Streptavidine-coated SPA beads (Amersham, Inc.)*, 5 mM EDTA, 0.1% Triton X-100 and 50 µM ATP, in phosphate saline buffer. After incubation for 60 minutes at RT, beads are sedimented by centrifugation at 1500 x g for 5 minutes, resuspended in 200 µl of PBS containing 5 mM EDTA, 0.1% Triton X-100 and 50 µM ATP and the radioactivity measured in a scintillation β counter, following sedimentation of the beads as described above. By substituting GST-c Jun for biotinylated GST-₁ATF₂ or myelin basic protein, this assay can be used to measure inhibition of preactivated p38 and ERK MAP Kinases, respectively.

<i>Exemple</i>	<i>JNK3</i>	<i>JNK2</i>	<i>p38</i>	<i>ERK2</i>
37	0.68	1.19	>30	>30
84	0.86	1.30	>30	>30
86	0.80	1.05	>30	>30
91	0.15	0.64	>30	>30
109	0.23	0.59	>30	>30
110	0.11	0.31	>30	>30
120	0.40	0.56	>30	>30
131	0.71	2.23	>30	>30

155	0.53	0.50	>30	>30
168	0.89	1.20	>30	>30
204	0.17	0.22	>30	>30
211	0.27	0.39	>30	>30
271	0.36	0.22	>30	>30
285	0.19	0.23	>30	>30

The values indicated in respect of JNK2 and 3, p38 and ERK2 refer to the IC₅₀ (μM), i.e. the amount necessary to achieve 50% inhibition of said target (e.g. JNK2). From the above table it could be derived that said test compounds according to formula I do have
5 a significant effect both on JNK2 and 3, but virtually no effect onto p38 and ERK2, thus delivering a quite selective inhibitory effect.

Sympathetic Neuron Culture and Survival Assay

10 Sympathetic neurons from superior cervical ganglia (SCG) of new-born rats (p4) are dissociated in dispase, plated at a density of 10⁴ cells/cm² in 48 well MTT plates coated with rat tail collagen, and cultured in Leibowitz medium containing 5% rat serum, 0.75 μg/mL NGF 7S (Boehringer Mannheim Corp., Indianapolis, IN.) and arabinosine 10⁻⁵M. Cell death is induced at day 4 after plating by exposing the culture to medium contain-
15 ing 10 μg/mL of anti NGF anti-body (Boehringer Mannheim Corp., Indianapolis, IN.) and no NGF or arabinosine, in the presence or absence of sulfonamide inhibitors. 24 hours after cell death induction, determination of cell viability is performed by incubation of the culture for 1 hour, at 37°C in 0.5 mg/mL of 3-(4,5-dimethylthiazol-2-yl)2,5 diphenyl tetrazolium bromide (MTT). After incubation in MTT cells are resuspended in
20 DMSO, transferred to a 96 MTT plate and cell viability is evaluated by measuring optical density at 590 nm.

The results of this assay with various test compounds demonstrate that compounds of Formula I are rescuing neurons from cells death (% neurons alive between 10 and 80)

IL-2 Release Assay:

Jurkat cells, a human T cell leukemia cell line (American Type Culture Collection # TIB 152) were cultured in RPMI 1640 medium (Gibco, BRL) supplemented with 10% of heat-activated FCS, Glutamine and Penstrep. The cell suspension in the medium is diluted to give $2 \cdot 10^6$ cells/mL. The cells were plated ($2 \cdot 10^5$ cells/well) on a 96-well plate containing different concentration of test compound (final concentration of compounds, 10, 3, 1, 0.3, 0.1 μ M). This mixture is incubated 30 minutes at 37°C in a humidified CO₂ atmosphere. Cells were then treated with 10 μ l PMA + Ionomycine (0.1 μ M and 1 μ M final concentration) in all wells except negative control. In wells without compounds, 10 μ l of RPMI 2% DMSO (=0.1% final) is added. Cells are incubated 24 hours at 37°C and then the supernatant harvested (freeze at -20°C if not used the same day) prior to performing IL-2 ELISA test on the supernatant.

IL-2 ELISA Assay:

IL-2 release into the medium by PMA+Iono-stimulated Jurkat cells, in presence or absence of test compounds is assayed by ELISA. Following the procedure described below

Solutions

Wash buffer: PBS- Tween 0.05%

Diluent: PBS- Tween 0.05%

Substrate solution: Citric acid 0.1M/Na₂HPO₄ 0.1M

Stop solution: H₂SO₄ 20%

Matched Antibody pairs/ standard:

From R&D Systems

Monoclonal anti-human IL-2 antibody (MAB602) (capture)

Biotinylated anti-human IL-2 antibody (BAF202) (detection)

Recombinant human IL-2 (202-IL-010) (standard)

Plate preparation

Transfer 100 μ l capture antibody diluted in PBS at 5 μ g/mL into a 96 well ELISA plate and incubate overnight at room temperature.

Aspirate each well and wash 3 times with Wash buffer. After the last wash, damp the plate.

1. Saturate with 200 μ l PBS-10% FCS. Incubate 1 hour at room temperature.
2. Repeat the wash step 2.

Assay procedure

1. Add 100 μ l of sample or standard (2000, 1000, 500, 250, 125, 62.5, 31.25pg/mL)
5 and incubate 2 hours at room temperature.
2. Wash 3 times.
3. Add 100 μ l of biotinylated anti-human IL-2 at 12.5 ng/mL. Incubate 2 hours at room temperature.
4. Wash 3 times.
- 10 5. Add 100 μ l streptavidin-HRP (Zymed #43-4323) at 1:10'000. Incubate 30 minutes at room temperature.
6. Wash 3 times
7. Add 100 μ l substrate solution (citric acid/ Na_2HPO_4 (1:1) + H_2O_2 1:2000 + OPD). Incubate 20-30 minutes at room temperature.
- 15 8. Add 50 μ l of stop solution to each well.
9. Determine optical density using a microtiter plate reader set to 450 nm with correction at 570 nm.

The result of this assay with various test compounds is summarized below:

20

<i>Exemple</i>	<i>% Inhibition of IL2 Production @3uM</i>
37	> 30
84	> 30
86	> 30
91	> 30
109	> 30
110	> 30
120	> 30
131	> 30
155	> 30



168	> 30
204	> 30
211	> 30
271	> 30
285	> 30

C-Jun Reporter Assay

Cell culture

- 5 Hlr c-Jun HeLa cells are cultured in DMEM High Glc supplemented with 10% FCS (Sigma), 2mM Glutamine (Gibco), P/S, Hygromycin b 100µg/mL and G418 250µg/mL

Cell culture preparation

Cell Banks

- The cells are stored frozen in cryotubes under liquid nitrogen, as 1.8 mL volumes of cell
10 suspension in culture medium containing 10% dimethyl sulfoxide.

Cells are kept in culture for no more than 20 passages.

Cell culture thawing

- When necessary, frozen vials of cells are thawed rapidly at 37°C in a water bath by
gently swirling up to semi-complete thawing. Then the cell suspension are added to 10
15 mL of culture medium.

The cell suspension is then centrifuged for 5 minutes at 1200 rpm, the supernatant is removed and the cell pellet reconstituted in the medium and add to a 175 cm² flask containing 25 mL medium. The flasks are incubated at 37° C in an atmosphere of 5 % CO₂.

- 20 ***Cell passage***

The cells are serially subcultured (passaged) when 80% confluent monolayers have been obtained.

The medium of each flask is removed and the monolayer is washed with 10-15 mL of phosphate buffer solution (PBS).

- 25 Trypsin-EDTA solution is added to the cell monolayer, incubated at 37° C and tapped gently at intervals to dislodge the cells. Complete detachment and disaggregation of the



cell monolayer is confirmed by microscopy examination. The cells are then resuspended in 10 mL of complete medium and centrifuged for 5 minutes at 1200 rpm.

The supernatant are discarded, the cells are resuspended in culture medium and diluted 1/5 in 175 cm² flasks.

5 ***Day 0 morning***

Prepare cells for transfections

The cells from flasks of near-confluent cultures are detached and disaggregated by treatment with trypsin as described above.

The cells are resuspended in culture medium and counted.

- 10 The cell suspension are diluted with medium to give about 3.5×10^6 cells/mL and 1 mL μ l of cell suspension are put onto 2 10cm culture dishes containing 9 mL of culture medium.

The plates are incubated at 37° C in a humidified atmosphere of 5 % CO₂ in air

Day 0 evening

15 **Transfections**

Control :0.2 μ g pTK Renilla, 5.8 μ g pBluescript KS, 500 μ l OPTIMEM (GIBCO),
18 μ l Fugene 6

- Induced :0.1 μ g pMEKK1, 0.2 μ g pTK Renilla, 5.7 μ g pBluescript KS, 500 μ l
20 OPTIMEM (GIBCO), 18 μ l Fugene 6 30' RT

The transfection mixture is added to the plated cells. The plates are incubated over night at 37° C in a humidified atmosphere of 5 % CO₂ in air

Day 1

A 96 wells plate containing 100 μ l of culture medium per well is prepared

- 25 Negative control (vehicle): 2 μ l of DMSO is added to the 100 μ l(in triplicate).

Compound : 2 μ l of Hit compound stock dilution are added to the 100 μ l(in triplicate).

The transfected cells are trypsinised and resuspend in 12 mL of culture medium.

100 μ l of the dilution are added to each of the 96 wells plate.

The plate is incubated over night at 37° C in a humidified atmosphere of 5 % CO₂ in air

- 30 ***Hit compound dilutions***

Hit compound stock concentrations are the following:

3, 1 and 0.1mM in 100% DMSO.



Day 2

Test procedure

Dual-Luciferase™ Reporter Assay System (Promega)

- 5 The medium is removed from the plate and the cells washed two times with 100µl PBS. Completely remove the rinse solution before applying PLB reagent. Dispense into each culture well 5µl of 1X PLB. Place the culture plates on a rocking platform or orbital shaker with gentle rocking/shaking to ensure complete and even coverage of the cell monolayer with 1X PLB.
- 10 Rock the culture plates at room temperature for 15 minutes. Transfer 20 µl of the lysate into a white opaque 96 wells plate. Read in a luminometer.
 - Inject 50µl of Luciferase Assay Reagent II wait 5'', read 10''
 - Inject 50µl of Stop & Glo ® Reagent wait 5'', read 10''
- 15 Check RLU Luciferase/RLU Renilla*1000

The result of this assay with various test compounds is summarized below:

<i>Exemple</i>	<i>% inhibition @10uM</i>
37	> 30
84	> 30
86	> 30
91	> 30
109	> 30
110	> 30
120	> 30
131	> 30
155	> 30
168	> 30



204	> 30
211	> 30
271	> 30
285	> 30

LPS induced Endotoxin Shock in Mice

The ability of the JNK inhibitors described in formula I to significantly reduce the level of inflammatory cytokines induced by LPS challenge was assessed using the following protocol:

5 LPS (S. abortus-Galanos Lab.-) was injected (200 µg/kg, i.v.) to Male C57BL/6 to induce endotoxin shock and compounds (0.1, 1, 10 mg/kg) or NaCl (200uM) were injected intravenously (10 mL/kg) 15 min before the LPS challenge. Heparinized blood was obtained from the orbital sinus at different time points after the LPS challenge, and
10 the blood was centrifuged at 9'000 rpm for 10 min at 4⁰ C to collect supernatant for the measurement of cytokines production by mouse ELISA kit such as IFN γ (DuoSet R&D Ref. DY485). The test compounds displayed considerable capability to reduce inflammatory related cytokines.

15 Global Ischemia in Gerbils

The ability of the JNK inhibitors described in formula I to protect cell death during a stroke event was assessed using the following protocol:

-1- METHOD

*** Surgery**

- 20 - Anesthesia: halothane or isoflurane (0.5-4%).
- Sheaving of the gorge and incision of the skin.
- The common carotid arteries (left and right) are freed from tissue.
- Occlusion of the arteries using Bulldog microclamps during 5 min.
- Disinfection of the surgery plan (Betadine®) and suture of the skin (Autoclip® ou
25 Michel's hooks).
- Stabulation of the animals under heating lamp until awake.
- Stabulation of the animals in the animalry in individual cages.



* Sacrifice of the animals

- 7 days after ischemia (Decapitation or overdose of pentobarbital).
- Sampling of the brain.

5

* Histological parameters

- Freezing of the brain in isopentane (-20°C)
- Slicing of the hippocampus using a cryo-microtome (20 µm).
- Staining with cresyl violet and/or TUNEL method
- Evaluation of the lesions (in CA1/CA2 subfields of the hippocampus)
 - Gerhard & Boast score modified or
 - Cell counting in the CA1/CA2

10

* Biochemical parameters

- Microdissection of the cerebral structures
- Parameters determined: DNA fragmentation, lactate, calcium penetration.
- Analytical methods: ELISA, colorimetry, enzymology, radiometry.

15

-2- TREATMENT

- Administration of the test article or the vehicle: 15 min after reperfusion (5-10 min after the recovery of the anesthesia).

20

- Standard protocol

50 animals : 5 groups of 10 (group A : control, groups B-D : test article at 3 doses and group E : reference compound (ketamine 3x120 mg/kg, *ip* or Orotic acid 3x300 mg/kg, *ip*).

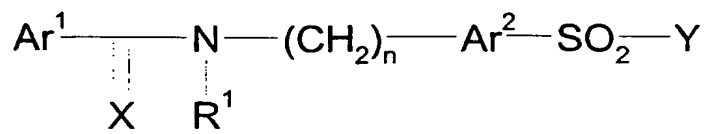
25

The test compounds displayed considerable capability to protect from neuronal apoptosis during induced global ischemia.



Claims

1. Sulfonamide derivatives according to formula I



I

with its geometrical isomers, in an optically active form as enantiomers, diastereomers, as well as in the form of racemates, as well as pharmaceutically acceptable salts thereof, wherein

Ar¹ and Ar² are independently from each other substituted or unsubstituted aryl or heteroaryl groups,

X is O or S, preferably O;

R¹ is hydrogen or a C₁-C₆-alkyl group, or R¹ forms a substituted or unsubstituted 5-6-membered saturated or unsaturated ring with Ar¹;

n is an integer from 0 to 5, preferably between 1-3 and most preferred 1;

Y within formula I is an unsubstituted or a substituted 4-12-membered saturated cyclic or bicyclic alkyl containing at least one nitrogen atom, whereby one nitrogen atom within said ring is forming a bond with the sulfonyl group of formula I thus providing a sulfonamide,

with the proviso that if Ar¹ is 4-chlorophenyl, X is O, R¹ is H, Ar² is thienyl, while Y is a piperazino group, L¹ shall not be diphenylmethyl, benzo[1,3]dioxol-5-yl-methyl, 4-methoxy phenyl, 2-hydroxyethyl, methyl, 4-chlorophenyl methyl, and if Y is a 3-methyl piperazino, L¹ shall not be 4-chlorophenyl methyl, and if Y is piperazino-3, 5-dione, L¹ shall not be 2-phenyl ethyl,

with the further proviso that if Ar¹ is 4-chlorophenyl, X is O, R¹ is H, Ar² is thienyl, while Y is a piperidino group with L¹ being H, L² shall not be 2-hydroxy ethyl;

with the further proviso that if Y is a piperidino- or a pyrrolidino group being substituted at the β-position of the piperidino- or a pyrrolidino nitrogen by a benzo[5, 6]cyclohepta[1, 2b]pyridine, or a benzo[5, 6]cyclohept (3,4) ene [1, 2b]pyridine, while Ar² is thienyl, X is oxygen, R¹ is hydrogen and n is 1, Ar¹ shall not be a phenyl group;

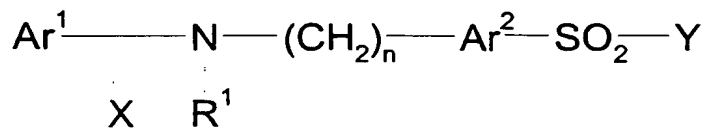


with the further proviso that if X is oxygen, R¹ is hydrogen and n is 1, while Y is a piperazine, said piperazine at the para-nitrogen shall not be substituted by a group containing a benzamidine or a protected form thereof;

with the further proviso that the compounds 2-{[2-(benzoylaminomethyl)-thiophene]-5-sulfonyl}-1,2,3,5,6,7-hexahydro-N,N-dipropylcyanopent[f]isoin-
dol-6-amine and N-[[5-[[7-cyano-1,2,3,5-tetrahydro-1-(1H-imidazol-4-yl-
methyl)-3-(phenylmethyl)-4H-1,4-benzodiazepin-4-yl]sulfonyl]-2-thienyl]
methyl] benzamide and its hydrochloride are excluded;

with the final proviso that if X is oxygen and Y is a 4-8 membered saturated cy-
clic alkyl containing one or two nitrogen atoms, Y shall not be substituted by a
group (C=O)N(R,R') at the α-position of the sulfonamide nitrogen.

2. Sulfonamide derivatives according to formula I



with its geometrical isomers, in an optically active form as enantiomers, dia-
stereomers, as well as in the form of racemates, as well as pharmaceutically ac-
ceptable salts thereof, wherein

Ar¹ and Ar² are independently from each other substituted or unsubstituted aryl
or heteroaryl groups,

X is O or S, preferably O;

R¹ is hydrogen or a C₁-C₆-alkyl group, or R¹ forms a substituted or unsubstituted
5-6-membered saturated or unsaturated ring with Ar¹;

n is an integer from 0 to 5, preferably between 1-3 and most preferred 1;

Y within formula I is an unsubstituted or a substituted 4-12-membered saturated
cyclic or bicyclic alkyl containing at least one nitrogen atom, whereby one ni-
trogen atom within said ring is forming a bond with the sulfonyl group of for-
mula I thus providing a sulfonamide, for use as a medicament;

with the proviso that if Y is a piperidino- or a pyrrolidino group being substitu-
ted at the β-position of the piperidino- or a pyrrolidino nitrogen by a benzo[5,
6]cyclohepta[1, 2b]pyridine, or a benzo[5, 6]cyclohept (3,4) ene [1, 2b]pyridine,

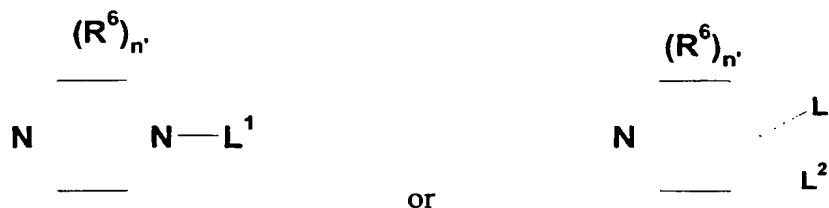
while Ar² is thienyl, X is oxygen, R¹ is hydrogen and n is 1, Ar¹ shall not be a phenyl group;

with the further proviso that if X is oxygen, R¹ is hydrogen and n is 1, while Y is a piperazine, said piperazine at the para-nitrogen shall not be substituted by a group containing a benzamidine or a protected form thereof;

with the further proviso that the compounds 2-{{2-(benzoylaminomethyl)-thiophene}-5-sulfonyl}-1,2,3,5,6,7-hexahydro-N,N-dipropylcyanopent[f]isoindol-6-amine and N-[[5-[[7-cyano-1,2,3,5-tetrahydro-1-(1H-imidazol-4-yl-methyl)-3-(phenylmethyl)-4H-1,4-benzodiazepin-4-yl]sulfonyl]-2-thienyl] methyl] benzamide and its hydrochloride are excluded;

with the final proviso that if X is oxygen and Y is a 4-8 membered saturated cyclic alkyl containing one or two nitrogen atoms, Y shall not be substituted by a group (C=O)N(R,R') at the α -position of the sulfonamide nitrogen.

3. A sulfonamide derivative according to claim 1 or 2, wherein Y is a piperazino-
or piperidino group of the general formula



whereby, L¹ and L² are independently selected from each other from the group comprising or consisting of H, substituted or unsubstituted C₁-C₆-aliphatic alkyl, substituted or unsubstituted C₂-C₆-alkenyl, substituted or unsubstituted C₂-C₆-alkynyl, substituted or unsubstituted cyclic C₄-C₈-alkyl optionally containing 1-3 heteroatoms and optionally fused with aryl or heteroaryl; or L¹ and L² are independently selected from the group comprising or consisting of substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, aryl-C₁-C₆-alkyl, heteroaryl-C₁-C₆-alkyl, -C(O)-OR³, -C(O)-R³, -C(O)-NR^{3'}R³, -NR^{3'}R³, -NR^{3'}C(O)R³, -NR^{3'}C(O)NR^{3'}R³, -(SO)R³, -(SO₂)R³, -NSO₂R³, -SO₂NR^{3'}R³, with R³, R^{3'} being substituents independently selected from the group comprising or consisting of H, substituted or unsubstituted C₁-C₆-alkyl, substituted or unsubstituted C₂-C₆-alkenyl, substituted or unsubstituted aryl, substituted or un-

substituted heteroaryl, substituted or unsubstituted aryl-C₁-C₆-alkyl, substituted or unsubstituted heteroaryl-C₁-C₆-alkyl;

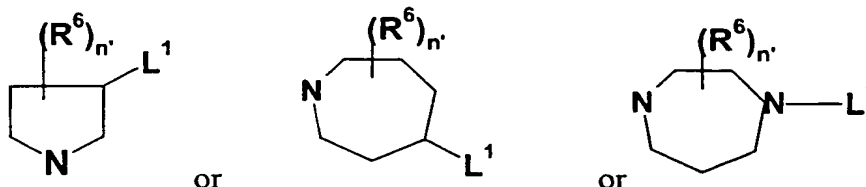
said aryl or heteroaryl groups being optionally substituted C₁-C₆-alkyl, C₁-C₆-alkoxy, C₂-C₆-alkenyl, C₂-C₆-alkynyl, amino, acylamino, aminocarbonyl, C₁-C₆-alkoxycarbonyl, aryl, carboxyl, cyano, halogen, hydroxy, nitro, sulfonyl, sulfoxy, C₁-C₆-thioalkoxy,

or L¹ and L² taken together form a 4-8-membered, substituted or unsubstituted saturated cyclic alkyl or heteroalkyl group; and

R⁶ is selected from the group comprising or consisting of hydrogen, substituted or unsubstituted C₁-C₆-alkyl, substituted or unsubstituted C₁-C₆-alkoxy, OH, halogen, nitro, cyano, sulfonyl, oxo (=O), and

n' is an integer from 0 to 4, preferably 1 or 2.

4. A sulfonamide derivative according to claim 1 or 2, wherein Y is a pyrrolidine, an azepan or a 1,4-diazepan moiety of the below formulas



wherein L¹ is selected from the group comprising or consisting of H, substituted or unsubstituted C₁-C₆-alkyl, substituted or unsubstituted C₂-C₆-alkenyl, substituted or unsubstituted C₂-C₆-alkynyl, substituted or unsubstituted cyclic C₄-C₈-alkyl optionally containing 1-3 heteroatoms and optionally fused with aryl or heteroaryl; or L¹ and L² are independently selected from the group comprising or consisting of substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, aryl-C₁-C₆-alkyl, heteroaryl-C₁-C₆-alkyl, -C(O)-OR³, -C(O)-R³, -C(O)-NR^{3'}R³, -NR^{3'}R³, -NR^{3'}C(O)R³, -NR^{3'}C(O)NR^{3'}R³, -(SO)R³, -(SO₂)R³, -NSO₂R³, -SO₂NR^{3'}R³;

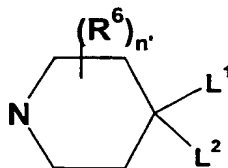
R³ and R^{3'} are substituents independently selected from the group comprising or consisting of H, substituted or unsubstituted C₁-C₆-alkyl, substituted or unsubstituted C₂-C₆-alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aryl-C₁-C₆-alkyl, substituted or unsubstituted heteroaryl-C₁-C₆-alkyl;



R^6 is selected from the group comprising or consisting of hydrogen, substituted or unsubstituted C_1 - C_6 -alkyl, substituted or unsubstituted C_1 - C_6 -alkoxy, OH, halogen, nitro, cyano, sulfonyl, oxo ($=O$), sulfoxy, acyloxy, thioalkoxy and n' is an integer from 0 to 4, preferably 0.

- 5 5. A sulfonamide derivative according to any of the preceding claims, wherein Ar^1 and Ar^2 are independently selected from the group comprising or consisting of phenyl, thienyl, furyl, pyridyl, optionally substituted by C_1 - C_6 -alkyl, preferably trihalomethyl, C_1 - C_6 -alkoxy, C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl, amino, acylamino, aminocarbonyl, C_1 - C_6 -alkoxycarbonyl, aryl, carboxyl, cyano, halogen, hydroxy,

10 nitro, sulfonyl, C_1 - C_6 -thioalkoxy.
6. A sulfonamide derivative according to claim 5, wherein Ar^1 is an unsubstituted or substituted phenyl.
7. A sulfonamide derivative according to claim 5, wherein Ar^2 is an unsubstituted or substituted thienyl or furanyl group.
- 15 8. A sulfonamide derivative according to any of the preceding claims, wherein Ar^1 is selected from a 4-chlorophenyl, nitrophenyl, hydroxyphenyl, alkoxy phenyl, pyridyl, 3,4,-dihydroxyphenyl, thioxo-dihydropyridine or its tautomer, pyrazole and X is O, R^1 is hydrogen, n is 1, Ar^2 is thienyl or furanyl.
9. A sulfonamide derivative according to claim 8, wherein Y is



20

with $(R^6)_n$, L^1 and L^2 being as above defined.

10. A sulfonamide derivative according to claim 9, wherein R^6 is H, L^2 is H, L^1 is a 5-membered cyclic group containing 3 heteroatoms, preferably a triazole ring which is preferably fused with an unsubstituted or substituted aryl or heteroaryl;

25 or L^1 is $-C(O)-R^3$, or $-NHR^3$;



with R³ being a substituent selected from the group comprising or consisting of C₁-C₁₂-alkyl, aryl, heteroaryl, aryl-C₁-C₆-alkyl, heteroaryl-C₁-C₆-alkyl; said aryl or heteroaryl groups being optionally substituted by halogen, hydroxy, nitro, sulfonyl.

- 5 11. A sulfonamide derivative according to any of the preceding claims selected from the following group :

4-chloro-N-[5-(piperazine-1-sulfonyl)-thiophen-2-yl-methyl]-benzamide

4-Chloro-N-{5-[4-(3-trifluoromethanesulfonyl-phenylamino)-piperidine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

10 4-chloro-N-({5-[(4-pyridin-2-ylpiperazin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

4-chloro-N-[(5-{[4-(4-fluorobenzoyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

15 4-chloro-N-{{5-({4-[4-(trifluoromethyl)phenyl]piperazin-1-yl}sulfonyl)thien-2-yl}methyl}benzamide

4-chloro-N-({5-[(4-{2-nitrophenyl}piperazin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

4-chloro-N-({5-[(4-{4-nitrophenyl}piperazin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

20 4-chloro-N-[(5-{[4-(2-furoyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

4-chloro-N-[(5-{[4-(4-hydroxyphenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide_

25 4-chloro-N-[(5-{[4-(2-oxo-2-pyrrolidin-1-ylethyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

4-chloro-N-[(5-{[4-(2-morpholin-4-yl-2-oxoethyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

4-chloro-N-[(5-{[4-(pyridin-4-ylmethyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

30 4-chloro-N-[(5-{[4-(2-thien-2-ylethyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide



- 4-chloro-N-[(5-{[4-(3,5-dimethoxyphenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 4-chloro-N-[(5-{[4-(cyclohexylmethyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 5 4-chloro-N-[(5-{[4-(2-methoxyphenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- N-({5-[(4-benzylpiperazin-1-yl)sulfonyl]thien-2-yl}methyl)-4-chlorobenzamide
- 4-chloro-N-[(5-{[4-(2-phenylethyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 10 4-chloro-N-[(5-{[4-(4-fluorobenzyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 4-chloro-N-[(5-{[4-(2-cyanophenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 4-chloro-N-({5-({4-[4-chloro-3-(trifluoromethyl)phenyl]piperazin-1-yl}sulfonyl)thien-2-yl}methyl}benzamide
- 15 4-chloro-N-[(5-{[4-(3-piperidin-1-ylpropyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 4-chloro-N-({5-[(4-{4-chloro-2-nitrophenyl}piperazin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide
- 20 4-chloro-N-[(5-{[4-(6-methylpyridin-2-yl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 4-chloro-N-({5-[(4-hydroxy-4-phenylpiperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide
- N-({5-[(4-benzoylpiperidin-1-yl)sulfonyl]thien-2-yl}methyl)-4-chlorobenzamide
- 25 4-chloro-N-[(5-{[4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- N-({5-[(4-benzylpiperidin-1-yl)sulfonyl]thien-2-yl}methyl)-4-chlorobenzamide
- 4-chloro-N-({5-[(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-8-yl)sulfonyl]thien-2-yl}methyl)benzamide
- 30 4-chloro-N-({5-({4-[2-(methylanilino)-2-oxoethyl]piperazin-1-yl}sulfonyl)thien-2-yl}methyl}benzamide

- 4-chloro-N-{{5-({4-[hydroxy(diphenyl)methyl]piperidin-1-yl}sulfonyl)thien-2-yl)methyl}benzamide
- 4-chloro-N-[(5-{{4-(3-cyanopyrazin-2-yl)piperazin-1-yl}sulfonyl}thien-2-yl)methyl]benzamide
- 5 4-chloro-N-({5-[(4-{5-nitropyridin-2-yl}piperazin-1-yl)sulfonyl]thien-2-yl)methyl}benzamide
- 4-chloro-N-{{5-({4-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}sulfonyl)thien-2-yl)methyl}benzamide
- 4-chloro-N-{{5-({4-[5-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}sulfonyl)thien-2-yl)methyl}benzamide
- 10 4-chloro-N-{{5-({4-[3-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}sulfonyl)thien-2-yl)methyl}benzamide
- 4-chloro-N-[(5-{{4-(2,4-difluorobenzoyl)piperidin-1-yl}sulfonyl}thien-2-yl)methyl]benzamide
- 15 methyl 5-{4-[(5-{{(4-chlorobenzoyl)amino}methyl}thien-2-yl)sulfonyl]piperazin-1-yl}-7-(trifluoromethyl)thieno[3,2-b]pyridine-3-carboxylate
- ethyl 2-{4-[(5-{{(4-chlorobenzoyl)amino}methyl}thien-2-yl)sulfonyl]piperazin-1-yl}-5-cyano-6-methylnicotinate
- 20 4-chloro-N-{{5-({4-[5-cyano-4,6-bis(dimethylamino)pyridin-2-yl]piperazin-1-yl}sulfonyl)thien-2-yl)methyl}benzamide
- 4-chloro-N-{{5-({4-[6-methyl-2-(trifluoromethyl)quinolin-4-yl]piperazin-1-yl}sulfonyl)thien-2-yl)methyl}benzamide
- tert-butyl 4-[(5-{{(4-chlorobenzoyl)amino}methyl}thien-2-yl)sulfonyl]piperazine-1-carboxylate
- 25 2-{4-[(5-{{(4-chlorobenzoyl)amino}methyl}thien-2-yl)sulfonyl]piperazin-1-yl}-8-ethyl-5-oxo-5,8-dihydropyrido[2,3-d]pyrimidine-6-carboxylic acid
- 7-{4-[(5-{{(4-chlorobenzoyl)amino}methyl}thien-2-yl)sulfonyl]piperazin-1-yl}-1-ethyl-6-fluoro-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylic acid
- 30 7-{4-[(5-{{(4-chlorobenzoyl)amino}methyl}thien-2-yl)sulfonyl]piperazin-1-yl}-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

- 4-chloro-N-[(5-{[4-(2,3-dihydro-1,4-benzodioxin-2-ylcarbonyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 4-chloro-N-{[5-({4-[(2E)-3-phenylprop-2-enyl]piperazin-1-yl} sulfonyl)thien-2-yl)methyl}benzamide
- 5 4-chloro-N-[(5-{[4-(3-phenylpropyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 4-chloro-N-[(5-{[4-(3,4,5-trimethoxyphenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 10 N-[(5-{[4-(4-tert-butylbenzyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide
- 4-chloro-N-[(5-{[4-(4-fluorophenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 4-chloro-N-[(5-{[4-(2-hydroxyphenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 15 4-chloro-N-{[5-({4-[4-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl} sulfonyl)thien-2-yl)methyl}benzamide
- 4-chloro-N-[(5-{[4-(5-cyanopyridin-2-yl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- tert-butyl 1-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperidin-4-ylcarbamate
- 20 4-chloro-N-({5-[(4-phenylpiperazin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide
- 4-chloro-N-{[5-(piperidin-1-ylsulfonyl)thien-2-yl)methyl}benzamide
- 4-chloro-N-[(5-{[4-(1-naphthyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 25 4-chloro-N-[(5-{[4-(3,4-dichlorophenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 4-chloro-N-{[5-({4-[3-(trifluoromethyl)phenyl]piperazin-1-yl} sulfonyl)thien-2-yl)methyl}benzamide
- 4-chloro-N-{[5-({3-hydroxy-4-[3-(trifluoromethyl)phenyl]piperidin-1-yl} sulfonyl)thien-2-yl)methyl}benzamide
- 30 4-chloro-N-[(5-{[4-(2-methylphenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide

- N-[(5-{[(1R,4R)-5-benzyl-2,5-diazabicyclo[2.2.1]hept-2-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide
- N-[(5-{[4-(benzyloxy)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide
- 5 4-chloro-N-[(5-{[4-(2-chlorodibenzo[b,f][1,4]oxazepin-11-yl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- N-(4-chlorophenyl)-2-(5-{[4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)acetamide
- 4-chloro-N-(5-{[4-(4-hydroxypiperidin-1-yl)sulfonyl]thien-2-yl)methyl}benzamide
- 10 N-[(5-{[4-(4-acetylphenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide
- 4-chloro-N-[(5-{[4-(3,5-dichloropyridin-4-yl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 15 4-chloro-N-[(5-{[4-(3-methoxyphenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- N-(5-{[4-(4-benzyl-4-hydroxypiperidin-1-yl)sulfonyl]thien-2-yl)methyl}-4-chlorobenzamide
- N-{[5-(4-{[2-tert-butyl-1H-indol-5-yl]amino}piperidin-1-yl)sulfonyl]thien-2-yl)methyl}-4-chlorobenzamide
- 20 4-chloro-N-{[5-(4-{[phenylacetyl]amino}piperidin-1-yl)sulfonyl]thien-2-yl)methyl}benzamide
- 4-chloro-N-[(5-{[4-(tetrahydrofuran-2-ylcarbonyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 25 4-chloro-N-[(5-{[4-(6-chloropyridin-2-yl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 4-chloro-N-[(5-{[4-(4-chlorophenyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- N-[(5-{[4-(2H-1,2,3-benzotriazol-2-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide
- 30 4-chloro-N-[(5-{[4-(4-chlorobenzoyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide



- 4-chloro-N-({5-[(4-phenoxy) piperidin-1-yl]sulfonyl}thien-2-yl)methyl)benzamide
- N-{{5-({4-[benzyl(methyl)amino]piperidin-1-yl}sulfonyl}thien-2-yl)methyl}-4-chlorobenzamide
- 5 4-chloro-N-{{5-({4-[3-(2,4-dichlorophenyl)-1H-pyrazol-5-yl]piperidin-1-yl}sulfonyl}thien-2-yl)methyl}benzamide
- 4-chloro-N-[(5-{{4-(5-thien-2-yl)-1H-pyrazol-3-yl}piperidin-1-yl}sulfonyl}thien-2-yl)methyl]benzamide
- 4-chloro-N-[(5-{{4-(2,3,4,5,6-pentamethylbenzoyl)piperidin-1-yl}sulfonyl}thien-2-yl)methyl]benzamide
- 10 4-chloro-N-[(5-{{4-(phenylacetyl)-1,4-diazepan-1-yl}sulfonyl}thien-2-yl)methyl]benzamide
- 4-chloro-N-{{5-({4-[5-(4-methoxyphenyl)-1H-pyrazol-3-yl]piperidin-1-yl}sulfonyl}thien-2-yl)methyl}benzamide
- 15 N-({5-[(4-anilinopiperidin-1-yl) sulfonyl]thien-2-yl)methyl)-4-chlorobenzamide
- 4-chloro-N-[(5-{{4-(3-phenyl-1,2,4-thiadiazol-5-yl)piperazin-1-yl}sulfonyl}thien-2-yl)methyl]benzamide
- 4-chloro-N-[(5-{{4-(2-phenylethyl)piperidin-1-yl}sulfonyl}thien-2-yl)methyl]benzamide
- 20 4-chloro-N-({5-[(4-heptylpiperazin-1-yl) sulfonyl]thien-2-yl)methyl)benzamide
- 4-chloro-N-({5-[(4-octylpiperazin-1-yl) sulfonyl]thien-2-yl)methyl)benzamide
- N-[(5-{{4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl}sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide
- 2-(5-{{4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl}sulfonyl}thien-2-yl)-N-(4-chlorophenyl)acetamide
- 25 2-{1-[(5-{{(4-chlorobenzoyl)amino}methyl}thien-2-yl)sulfonyl]piperidin-4-yl}-2H-1,2,3-benzotriazole-5-carboxylic
- 4-chloro-N-[(5-{{4-(5-chloro-1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl}sulfonyl}thien-2-yl)methyl]benzamide
- 30 methyl 1-{1-[(5-{{(4-chlorobenzoyl)amino}methyl}thien-2-yl)sulfonyl]piperidin-4-yl}-1H-1,2,3-benzotriazole-5-carboxylate

- methyl 1-{1-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperidin-4-yl}-1*H*-1,2,3-benzotriazole-6-carboxylate
- methyl 2-{1-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperidin-4-yl}-2*H*-1,2,3-benzotriazole-5-carboxylate
- 5 4-chloro-N-[(5-{[4-(6-chloro-1*H*-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 4-chloro-N-{[5-(4-[5-(trifluoromethyl)-1*H*-1,2,3-benzotriazol-1-yl]piperidin-1-yl)sulfonyl]thien-2-yl)methyl}benzamide
- N-[(5-{[4-(7-aza-1*H*-benzimidazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide
- 10 1-{1-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperidin-4-yl}-1*H*-1,2,3-benzotriazole-5-carboxylic
- 1-{1-[(5-{[(4-chlorobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperidin-4-yl}-1*H*-1,2,3-benzotriazole-6-carboxylic
- 15 N-[(5-{[4-(2-amino-9*H*-purin-9-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide
- 4-chloro-N-[(5-{[4-(9*H*-purin-9-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- N-[(5-{[4-(6-amino-9*H*-purin-9-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide
- 20 4-chloro-N-({5-[(4-{6-nitro-1*H*-benzimidazol-1-yl})piperidin-1-yl]sulfonyl}thien-2-yl)methyl)benzamide
- 4-chloro-N-({5-[(4-{5-nitro-1*H*-benzimidazol-1-yl})piperidin-1-yl]sulfonyl}thien-2-yl)methyl)benzamide
- 25 4-chloro-N-[(5-{[4-(2*H*-1,2,3-triazol-2-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- N-[(5-{[4-(1*H*-benzimidazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide
- 4-chloro-N-{[5-(4-[3-propylanilino]piperidin-1-yl)sulfonyl]thien-2-yl)methyl}benzamide
- 30 4-chloro-N-{[5-(4-[3-(trifluoromethyl)anilino]piperidin-1-yl)sulfonyl]thien-2-yl)methyl}benzamide

- 4-chloro-N- {[5-({4-[3-(dimethylamino)anilino]piperidin-1-yl} sulfonyl)thien-2-yl)methyl} benzamide
methyl
- 5 4-chloro-N- {[5-({4-[3-(methylsulfonyl)anilino]piperidin-1-yl} sulfonyl)thien-2-yl)methyl} benzamide
- 4-chloro-N-({5-[(4- {3-nitroanilino} piperidin-1-yl) sulfonyl] thien-2-yl} methyl) benzamide
- 4-chloro-N- [(5- { [4-(2-methoxyanilino) piperidin-1-yl] sulfonyl } thien-2-yl) methyl] benzamide
- 10 3-({ 1- [(5- { [(4-chlorobenzoyl) amino] methyl } thien-2-yl) sulfonyl] piperidin-4-yl } amino) benzamide
- 4-chloro-N- {[5-({4-[2-(trifluoromethyl)anilino]piperidin-1-yl} sulfonyl)thien-2-yl)methyl} benzamide
- 4-chloro-N-({5-[(4- {2-nitro-4-[(trifluoromethyl)sulfonyl]anilino} piperidin-1-yl) sulfonyl] thien-2-yl } methyl) benzamide
- 15 4-chloro-N- [(5- { [4-(4-chloroanilino) piperidin-1-yl] sulfonyl } thien-2-yl) methyl] benzamide
- 4-chloro-N- {[5-({4-[4-(trifluoromethyl)anilino]piperidin-1-yl} sulfonyl)thien-2-yl)methyl} benzamide
- 20 4-chloro-N-({5-[(4- {4-[(trifluoromethyl)sulfonyl]anilino} piperidin-1-yl) sulfonyl] thien-2-yl } methyl) benzamide
- 4-chloro-N-({5-[(4- {2-nitroanilino} piperidin-1-yl) sulfonyl] thien-2-yl } methyl) benzamide
- N- {[5-({4-[4-(aminocarbonyl)anilino]piperidin-1-yl} sulfonyl)thien-2-yl)methyl} -4-chlorobenzamide
- 25 4-chloro-N- {[5-({4-[4-(1,3-dithiolan-2-yl)anilino]piperidin-1-yl} sulfonyl)thien-2-yl)methyl} benzamide
- N- [(5- { [4-(3-chloroanilino) piperidin-1-yl] sulfonyl } thien-2-yl) methyl] -3-nitrobenzamide
- 30 4-chloro-N- [(5- { [4-(3-chloroanilino) piperidin-1-yl] sulfonyl } thien-2-yl) methyl] benzamide

- 4-chloro-N-[(5-{[4-(3-methoxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 4-chloro-N-{[5-(4-[3-(methylsulfonyl)anilino]piperidin-1-yl)sulfonyl]thien-2-yl)methyl}benzamide
- 5 N-({5-[(4-{3-[amino(imino)methyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl)methyl}-4-chlorobenzamide
- 4-chloro-N-({5-[(4-{3-[(2-hydroxyethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl)methyl}benzamide
- 10 N-[(5-{[4-(2-aminoanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide
- 4-chloro-N-[(5-{[4-(2-hydroxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 4-chloro-N-[(5-{[4-(4-hydroxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 15 4-chloro-N-({5-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl)methyl}benzamide
- 4-chloro-N-[(5-{[4-(3-toluidino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 4-chloro-N-({5-[(4-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]amino}piperidin-1-yl)sulfonyl]thien-2-yl)methyl}benzamide
- 20 4-chloro-N-{[5-(4-[3-(1,3-oxazol-5-yl)anilino]piperidin-1-yl)sulfonyl]thien-2-yl)methyl}benzamide
- N-[(5-{[4-(3-tert-butylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide
- 25 4-chloro-N-[(5-{[4-(2-propylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 4-chloro-N-{[5-(4-[(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)amino]piperidin-1-yl)sulfonyl]thien-2-yl)methyl}benzamide
- 4-chloro-N-[(5-{[4-(2,3-dihydro-1H-inden-5-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 30 4-chloro-N-[(5-{[4-(4-propylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide



- 4-chloro-N-[(5-{[4-(3-nitropyridin-2-yl)amino]piperidin-1-yl}sulfonyl}thien-2-yl)methyl]benzamide
- N-[(5-{[4-(3-aminopyridin-2-yl)amino]piperidin-1-yl}sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide
- 5 N-[(5-{[4-([1,1'-biphenyl]-3-ylamino)piperidin-1-yl}sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide
- N-[(5-{[4-(3-benzylanilino)piperidin-1-yl}sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide
- 4-chloro-N-[(5-{[4-(pyrimidin-2-ylamino)piperidin-1-yl}sulfonyl}thien-2-yl)methyl]benzamide
- 10 4-chloro-N-[(5-{[4-(morpholin-4-ylsulfonyl)anilino]piperidin-1-yl}sulfonyl}thien-2-yl)methyl]benzamide
- 4-chloro-N-[(5-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}piperidin-1-yl)sulfonyl]thien-2-yl)methyl]benzamide
- 15 4-chloro-N-[(5-{[4-(3-cyclohexyl-4-hydroxyanilino)piperidin-1-yl}sulfonyl}thien-2-yl)methyl]benzamide
- N-[(5-{[4-(butylamino)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl)methyl]-4-chlorobenzamide
- 4-chloro-N-[(5-{[4-(3-ethylanilino)piperidin-1-yl}sulfonyl}thien-2-yl)methyl]benzamide
- 20 4-chloro-N-[(5-{[4-(5,6,7,8-tetrahydronaphthalen-1-ylamino)piperidin-1-yl}sulfonyl}thien-2-yl)methyl]benzamide
- N-[(5-{[4-(3-(aminosulfonyl)anilino]piperidin-1-yl}sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide
- 25 4-chloro-N-[(5-{[4-(quinolin-5-ylamino)piperidin-1-yl}sulfonyl}thien-2-yl)methyl]benzamide
- 4-chloro-N-[(5-{[4-(quinolin-8-ylamino)piperidin-1-yl}sulfonyl}thien-2-yl)methyl]benzamide
- 4-Chloro-N-[(5-{[4-(3-propylphenoxy)piperidin-1-yl}sulfonyl}thien-2-yl)methyl]benzamide
- 30 4-chloro-N-[(5-{[4-[(2E)-3-phenylprop-2-enoyl]piperazin-1-yl}sulfonyl]thien-2-yl)methyl]benzamide



4-chloro-N-({5-[(4-{4-nitrobenzoyl}piperazin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

N-({5-[(4-benzoylpiperazin-1-yl)sulfonyl]thien-2-yl}methyl)-4-chlorobenzamide

5 4-chloro-N-{{5-({4-[4-(trifluoromethyl)benzoyl]piperazin-1-yl)sulfonyl}thien-2-yl)methyl}benzamide

4-chloro-N-{{5-({4-[4-(dimethylamino)benzoyl]piperazin-1-yl)sulfonyl}thien-2-yl)methyl}benzamide

10 4-chloro-N-[(5-{[4-(2-fluorobenzoyl)piperazin-1-yl)sulfonyl}thien-2-yl)methyl]benzamide

4-chloro-N-[(5-{[4-(2,6-difluorobenzoyl)piperazin-1-yl)sulfonyl}thien-2-yl)methyl]benzamide

4-chloro-N-[(5-{[4-(3-fluorobenzoyl)piperazin-1-yl)sulfonyl}thien-2-yl)methyl]benzamide

15 4-chloro-N-[(5-{[4-(2-naphthoyl)piperazin-1-yl)sulfonyl}thien-2-yl)methyl]benzamide

4-chloro-N-[(5-{[4-(1-naphthoyl)piperazin-1-yl)sulfonyl}thien-2-yl)methyl]benzamide

20 4-chloro-N-({5-[(4-{2-nitrobenzoyl}piperazin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide

4-chloro-N-[(5-{[4-(pyridin-3-ylcarbonyl)piperazin-1-yl)sulfonyl}thien-2-yl)methyl]benzamide

N-[(5-{[4-(2,1,3-benzoxadiazol-5-ylcarbonyl)piperazin-1-yl)sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide

25 4-chloro-N-[(5-{[4-(2,4-difluorobenzoyl)piperazin-1-yl)sulfonyl}thien-2-yl)methyl]benzamide

4-chloro-N-[(5-{[4-(2,4,6-trifluorobenzoyl)piperazin-1-yl)sulfonyl}thien-2-yl)methyl]benzamide

30 4-chloro-N-[(5-{[4-(2,6-dichlorobenzoyl)piperazin-1-yl)sulfonyl}thien-2-yl)methyl]benzamide

4-chloro-N-({5-[(4-heptanoylpiperazin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide



- 4-chloro-N-[(5-{[4-(quinolin-8-ylsulfonyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 4-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide
- 5 N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide
- 4-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide
- N-[(5-{[4-(2,4-difluorobenzoyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide
- 10 N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide
- N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide
- 15 4-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide
- N-[(5-{[4-(2,4-difluorobenzoyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide
- N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-nitrobenzamide
- 20 3-nitro-N-[(5-{[4-(3-methoxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 3-nitro-N-{{5-({4-[3-(trifluoromethyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl}methyl}benzamide
- 25 N-{{5-({4-[3-(dimethylamino)anilino]piperidin-1-yl}sulfonyl)thien-2-yl}methyl}-3-nitrobenzamide
- 3-nitro-N-{{5-({4-[3-(methylsulfonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl}methyl}benzamide
- 3-nitro-N-{{5-({4-[3-(methylsulfanyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl}methyl}benzamide
- 30 N-{{5-({4-[3-(aminosulfonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl}methyl}-3-nitrobenzamide



methyl

N-{{5-({4-[3-(aminocarbonyl)anilino]piperidin-1-yl} sulfonyl)thien-2-yl)methyl}-3-nitrobenzamide

3-nitro-N-({5-({4-[3-nitroanilino]piperidin-1-yl)sulfonyl}thien-2-yl)methyl)benzamide

3-nitro-N-({5-({4-(2-methoxyanilino)piperidin-1-yl}sulfonyl}thien-2-yl)methyl)benzamide

3-nitro-N-{{5-({4-[2-(trifluoromethyl)anilino]piperidin-1-yl} sulfonyl)thien-2-yl)methyl} benzamide

3-nitro-N-({5-({4-[2-nitroanilino]piperidin-1-yl)sulfonyl}thien-2-yl)methyl)benzamide

N-({5-({4-(4-chloroanilino)piperidin-1-yl}sulfonyl}thien-2-yl)methyl)-3-nitrobenzamide

3-nitro-N-{{5-({4-[4-(trifluoromethyl)anilino]piperidin-1-yl} sulfonyl)thien-2-yl)methyl} benzamide

3-nitro-N-({5-({4-[4-(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl}thien-2-yl)methyl)benzamide

N-{{5-({4-[4-(aminocarbonyl)anilino]piperidin-1-yl} sulfonyl)thien-2-yl)methyl}-3-nitrobenzamide

N-({5-({4-(3-propylanilino)piperidin-1-yl}sulfonyl}thien-2-yl)methyl)-3-nitrobenzamide

N-({5-({4-(3-chloroanilino)piperidin-1-yl}sulfonyl}thien-2-yl)methyl)-4-nitrobenzamide

4-nitro-N-({5-({4-(3-methoxyanilino)piperidin-1-yl}sulfonyl}thien-2-yl)methyl)benzamide

4-nitro-N-{{5-({4-[3-(trifluoromethyl)anilino]piperidin-1-yl} sulfonyl)thien-2-yl)methyl} benzamide

N-{{5-({4-[3-(dimethylamino)anilino]piperidin-1-yl} sulfonyl)thien-2-yl)methyl}-4-nitrobenzamide

4-nitro-N-({5-({4-(3-propylanilino)piperidin-1-yl}sulfonyl}thien-2-yl)methyl)benzamide



- 4-nitro-N-{{5-({4-[3-(methylsulfonyl)anilino]piperidin-1-yl} sulfonyl)thien-2-yl)methyl}benzamide
- 4-nitro-N-{{5-({4-[3-(methylsulfonyl)anilino]piperidin-1-yl} sulfonyl)thien-2-yl)methyl}benzamide
- 5 N-{{5-({4-[3-(aminosulfonyl)anilino]piperidin-1-yl} sulfonyl)thien-2-yl)methyl}-4-nitrobenzamide methyl
- 3-{{1-({5-({4-nitrobenzoyl} amino)methyl)thien-2-yl} sulfonyl)piperidin-4-yl}amino}benzamide
- 10 4-nitro-N-({5-({4-[3-nitroanilino]piperidin-1-yl} sulfonyl)thien-2-yl} methyl)benzamide
- 4-nitro-N-({5-({4-(2-methoxyanilino)piperidin-1-yl} sulfonyl)thien-2-yl} methyl)benzamide
- 4-nitro-N-{{5-({4-[2-(trifluoromethyl)anilino]piperidin-1-yl} sulfonyl)thien-2-yl)methyl}benzamide
- 15 4-nitro-N-({5-({4-[2-nitroanilino]piperidin-1-yl} sulfonyl)thien-2-yl} methyl)benzamide
- N-({5-({4-[4-chloroanilino]piperidin-1-yl} sulfonyl)thien-2-yl} methyl)-4-nitrobenzamide
- 20 4-nitro-N-{{5-({4-[4-(trifluoromethyl)anilino]piperidin-1-yl} sulfonyl)thien-2-yl)methyl}benzamide
- 4-nitro-N-({5-({4-({4-[(trifluoromethyl)sulfonyl]anilino} piperidin-1-yl) sulfonyl)thien-2-yl} methyl)benzamide
- N-{{5-({4-[4-(aminocarbonyl)anilino]piperidin-1-yl} sulfonyl)thien-2-yl)methyl}-4-nitrobenzamide
- 25 N-{{5-({4-[4-(1,3-dithiolan-2-yl)anilino]piperidin-1-yl} sulfonyl)thien-2-yl)methyl}-4-nitrobenzamide
- N-({5-({4-[3-[amino(imino)methyl]anilino} piperidin-1-yl) sulfonyl)thien-2-yl} methyl)-3-nitrobenzamide
- 30 N-({5-({4-[3-[(2-hydroxyethyl)sulfonyl]anilino} piperidin-1-yl) sulfonyl)thien-2-yl} methyl)-3-nitrobenzamide
- N-({5-({4-anilinopiperidin-1-yl) sulfonyl)thien-2-yl} methyl)-3-nitrobenzamide

- N-({5-[(4-{3-[(2-hydroxyethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl)methyl)-4-nitrobenzamide
- N-({5-[(4-anilinopiperidin-1-yl)sulfonyl]thien-2-yl)methyl)-4-nitrobenzamide
- N-({5-[(4-{3-[amino(imino)methyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl)methyl)-4-nitrobenzamide
- 5 3-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl)methyl)benzamide
- 4-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl)methyl)benzamide
- 10 3-nitro-N-[(5-{[4-({3-nitropyridin-2-yl)amino}piperidin-1-yl)sulfonyl}thien-2-yl)methyl]benzamide
- N-[[5-({4-[(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)amino]piperidin-1-yl)sulfonyl]thien-2-yl)methyl]-3-nitrobenzamide
- N-[(5-{[4-(2,3-dihydro-1H-inden-5-ylamino)piperidin-1-yl)sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide
- 15 3-nitro-N-[(5-{[4-(2-propylanilino)piperidin-1-yl)sulfonyl}thien-2-yl)methyl]benzamide
- 3-nitro-N-[(5-{[4-(4-propylanilino)piperidin-1-yl)sulfonyl}thien-2-yl)methyl]benzamide
- 20 N-[(5-{[4-(3-tert-butylanilino)piperidin-1-yl)sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide
- 3-nitro-N-[[5-({4-[3-(1,3-oxazol-5-yl)anilino]piperidin-1-yl)sulfonyl]thien-2-yl)methyl]benzamide
- 3-nitro-N-[(5-{[4-(2-phenylethyl)piperidin-1-yl)sulfonyl}thien-2-yl)methyl]benzamide
- 25 N-({5-[(4-{3-chloro-5-(trifluoromethyl)pyridin-2-yl)amino}piperidin-1-yl)sulfonyl]thien-2-yl)methyl)-3-nitrobenzamide
- N-[(5-{[4-([1,1'-biphenyl]-3-ylamino)piperidin-1-yl)sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide
- 30 N-[(5-{[4-(3-benzylanilino)piperidin-1-yl)sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide



- 3-nitro-N-{{5-({4-[3-(morpholin-4-ylsulfonyl)anilino]piperidin-1-yl} sulfonyl)thien-2-yl)methyl} benzamide
- 3-nitro-N-[(5-{{4-(3-propylphenoxy)piperidin-1-yl} sulfonyl} thien-2-yl)methyl]benzamide
- 5 4-nitro-N-[(5-{{4-(pyrimidin-2-ylamino)piperidin-1-yl} sulfonyl} thien-2-yl)methyl]benzamide
- N-{{5-({4-[(3-aminopyridin-2-yl)amino]piperidin-1-yl} sulfonyl)thien-2-yl)methyl}-4-nitrobenzamide
- 4-nitro-N-[(5-{{4-({3-nitropyridin-2-yl} amino)piperidin-1-yl} sulfonyl} thien-2-yl)methyl]benzamide
- 10 N-[(5-{{4-(2,3-dihydro-1H-inden-5-ylamino)piperidin-1-yl} sulfonyl} thien-2-yl)methyl]-4-nitrobenzamide
- 4-nitro-N-[(5-{{4-(2-propylanilino)piperidin-1-yl} sulfonyl} thien-2-yl)methyl]benzamide
- 15 4-nitro-N-[(5-{{4-(4-propylanilino)piperidin-1-yl} sulfonyl} thien-2-yl)methyl]benzamide
- N-[(5-{{4-(3-tert-butylanilino)piperidin-1-yl} sulfonyl} thien-2-yl)methyl]-4-nitrobenzamide
- 4-nitro-N-{{5-({4-[3-(1,3-oxazol-5-yl)anilino]piperidin-1-yl} sulfonyl)thien-2-yl)methyl} benzamide
- 20 4-nitro-N-[(5-{{4-(2-phenylethyl)piperidin-1-yl} sulfonyl} thien-2-yl)methyl]benzamide
- N-({5-[(4-{{3-chloro-5-(trifluoromethyl)pyridin-2-yl} amino} piperidin-1-yl) sulfonyl]thien-2-yl} methyl)-4-nitrobenzamide
- 25 N-[(5-{{4-([1,1'-biphenyl]-3-ylamino)piperidin-1-yl} sulfonyl} thien-2-yl)methyl]-4-nitrobenzamide
- N-[(5-{{4-(3-benzylanilino)piperidin-1-yl} sulfonyl} thien-2-yl)methyl]-4-nitrobenzamide
- 4-nitro-N-{{5-({4-[3-(morpholin-4-ylsulfonyl)anilino]piperidin-1-yl} sulfonyl)thien-2-yl)methyl} benzamide
- 30 N-[(5-{{4-(2-aminoanilino)piperidin-1-yl} sulfonyl} thien-2-yl)methyl]-3-nitrobenzamide



- 3-nitro-N-[(5-{[4-(pyrimidin-2-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- N-[(5-{[4-[(3-aminopyridin-2-yl)amino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide
- 5 N-[(5-{[4-{2-nitro-4-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide
- 3-nitro-N-[(5-{[4-(3-phenylpropyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 3-nitro-N-[(5-{[4-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 10 N-[(5-{[4-(3-cyclohexyl-4-hydroxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide
- N-[(5-{[4-{3-[(butylamino)sulfonyl]anilino}piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide
- 15 N-[(5-{[4-(3-ethylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide
- 3-nitro-N-[(5-{[4-(5,6,7,8-tetrahydronaphthalen-1-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 4-nitro-N-[(5-{[4-(3-propylphenoxy)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 20 N-[(5-{[4-(2,4-difluorobenzoyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide
- N-[(5-{[4-(2,4-difluorobenzoyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide
- 25 2-Hydroxy-N-[(5-{[4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide
- N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-2-hydroxybenzamide
- 30 N-[(5-{[4-(1,3-dithiolan-2-yl)anilino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-nitrobenzamide



- 3-methoxy-N-[(5-{{4-(3-methoxyanilino)piperidin-1-yl}sulfonyl}thien-2-yl)methyl]benzamide
- 3-methoxy-N-{{5-({4-[3-(trifluoromethyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl)methyl}benzamide
- 5 N-{{5-({4-[3-(dimethylamino)anilino]piperidin-1-yl}sulfonyl)thien-2-yl)methyl}-3-methoxybenzamide
- 3-methoxy-N-[(5-{{4-(3-propylanilino)piperidin-1-yl}sulfonyl}thien-2-yl)methyl]benzamide
- 3-methoxy-N-{{5-({4-[3-(methylsulfonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl)methyl}benzamide
- 10 2-yl)methyl}benzamide
- 3-methoxy-N-{{5-({4-[3-(methylsulfanyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl)methyl}benzamide
- N-{{5-({4-[3-(aminosulfonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl)methyl}-3-methoxybenzamide
- 15 methyl
- N-{{5-({4-[3-(aminocarbonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl)methyl}-3-methoxybenzamide
- 3-methoxy-N-[(5-{{4-(2-methoxyanilino)piperidin-1-yl}sulfonyl}thien-2-yl)methyl]benzamide
- 20 N-({5-[(4-{3-nitroanilino}piperidin-1-yl)sulfonyl]thien-2-yl)methyl}-3-methoxybenzamide
- 3-methoxy-N-{{5-({4-[2-(trifluoromethyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl)methyl}benzamide
- N-({5-[(4-{2-nitroanilino}piperidin-1-yl)sulfonyl]thien-2-yl)methyl}-3-methoxybenzamide
- 25 methyl
- N-{{5-({4-[4-(aminocarbonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl)methyl}-3-methoxybenzamide
- N-{{5-({4-[4-(1,3-dithiolan-2-yl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl)methyl}-3-methoxybenzamide
- 30 N-[(5-{{4-(3-chloroanilino)piperidin-1-yl}sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide



- N-[(5-{[4-(4-chloroanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide
- 3-methoxy-N-({5-[4-{4-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl]sulfonyl}thien-2-yl)methyl)benzamide
- 5 N-({5-[4-{3-[amino(imino)methyl]anilino}piperidin-1-yl)sulfonyl}thien-2-yl)methyl)-3-methoxybenzamide
- N-({5-[4-{3-[(2-hydroxyethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl}thien-2-yl)methyl)-3-methoxybenzamide
- 3-methoxy-N-({5-[4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl]sulfonyl}thien-2-yl)methyl)benzamide
- 10 N-({5-[4-anilinopiperidin-1-yl]sulfonyl}thien-2-yl)methyl)-3-methoxybenzamide
- 3-methoxy-N-({5-[4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl]sulfonyl}thien-2-yl)methyl)benzamide
- 15 N-[(5-{[4-(4-hydroxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide
- 3-nitro-N-({5-[4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl]sulfonyl}thien-2-yl)methyl)benzamide
- 4-nitro-N-({5-[4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl]sulfonyl}thien-2-yl)methyl)benzamide
- 20 N-[(5-{[4-(2-hydroxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide
- 3-methoxy-N-[(5-{[4-(pyrimidin-2-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 25 N-{{5-({4-[(3-aminopyridin-2-yl)amino]piperidin-1-yl)sulfonyl}thien-2-yl)methyl}-3-methoxybenzamide
- N-[(5-{[4-({3-nitropyridin-2-yl}amino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide
- N-{{5-({4-[(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)amino]piperidin-1-yl)sulfonyl}thien-2-yl)methyl}-3-methoxybenzamide
- 30 N-[(5-{[4-(2,3-dihydro-1H-inden-5-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide



- 3-methoxy-N-[(5-{[4-(2-propylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 3-methoxy-N-[(5-{[4-(4-propylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 5 N-[(5-{[4-(3-tert-butylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide
- N-({5-[4-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]amino}piperidin-1-yl]sulfonyl}thien-2-yl)methyl)-3-methoxybenzamide
- 3-methoxy-N-({5-([4-[3-(1,3-oxazol-5-yl)anilino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl}benzamide
- 10 N-[(5-{[4-([1,1'-biphenyl]-3-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide
- 3-methoxy-N-[(5-{[4-(3-propylphenoxy)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 15 3-methoxy-N-({5-([4-[3-(morpholin-4-ylsulfonyl)anilino]piperidin-1-yl]sulfonyl}thien-2-yl)methyl}benzamide
- 3-methoxy-N-[(5-{[4-(2-phenylethyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 20 N-[(5-{[4-(3-benzylanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide
- 3-methoxy-N-[(5-{[4-(3-phenylpropyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 3-methoxy-N-({5-([4-{[4-(trifluoromethyl)pyrimidin-2-yl]amino}piperidin-1-yl]sulfonyl}thien-2-yl)methyl}benzamide
- 25 N-[(5-{[4-(3-cyclohexyl-4-hydroxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide
- N-({5-[4-{[3-[(butylamino)sulfonyl]anilino}piperidin-1-yl]sulfonyl}thien-2-yl)methyl}-3-methoxybenzamide
- 30 N-[(5-{[4-(3-ethyl-anilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide
- 3-methoxy-N-[(5-{[4-(5,6,7,8-tetrahydronaphthalen-1-ylamino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide



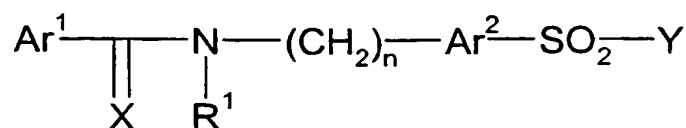
- N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-5-nitro-1H-pyrazole-3-carboxamide
- N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-2-oxo-1,2-dihydropyridine-3-carboxamide
- 5 N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-2-thioxo-1,2-dihydropyridine-3-carboxamide
- N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3,4-dihydroxybenzamide
- N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]pyridine-2-carboxamide
- 10 N-[(5-{[4-(hexyloxy)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide
- N-[(5-{[4-(heptanoyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-3-methoxybenzamide
- 15 4-chloro-N-[(5-{[4-(3-propylanilino)piperidin-1-yl]sulfonyl}-2-furyl)methyl]benzamide
- 4-chloro-N-[(5-{[4-(3-chloroanilino)piperidin-1-yl]sulfonyl}-2-furyl)methyl]benzamide
- 4-chloro-N-[(5-{[4-(3-methoxyanilino)piperidin-1-yl]sulfonyl}-2-furyl)methyl]benzamide
- 20 4-chloro-N-[(5-{[4-(3-(trifluoromethyl)anilino]piperidin-1-yl]sulfonyl}-2-furyl)methyl]benzamide
- 4-chloro-N-[(5-{[4-(3-(dimethylamino)anilino]piperidin-1-yl]sulfonyl}-2-furyl)methyl]benzamide
- 25 4-chloro-N-[(5-{[4-(3-(methylsulfonyl)anilino]piperidin-1-yl]sulfonyl}-2-furyl)methyl]benzamide
- 4-chloro-N-[(5-{[4-(3-(methylsulfanyl)anilino]piperidin-1-yl]sulfonyl}-2-furyl)methyl]benzamide
- 30 N-[(5-{[4-(3-(aminosulfonyl)anilino]piperidin-1-yl]sulfonyl}-2-furyl)methyl]-4-chlorobenzamide
- methyl 3-[(1-[(5-{[4-(4-chlorobenzoyl)amino]methyl}-2-furyl)sulfonyl]piperidin-4-yl)amino]benzoate



- 3-({1-[(5-[(4-chlorobenzoyl)amino]methyl}-2-furyl)sulfonyl]piperidin-4-yl}amino)benzamide
- 4-chloro-N-({5-[(4-{3-nitroanilino}piperidin-1-yl)sulfonyl]-2-furyl)methyl}benzamide
- 5 4-chloro-N-[(5-[(4-(2-methoxyanilino)piperidin-1-yl)sulfonyl]-2-furyl)methyl]benzamide
- 4-chloro-N-({5-[(4-[2-(trifluoromethyl)anilino]piperidin-1-yl)sulfonyl]-2-furyl)methyl}benzamide
- 4-chloro-N-({5-[(4-{2-nitroanilino}piperidin-1-yl)sulfonyl]-2-furyl)methyl}benzamide
- 10 4-chloro-N-[(5-[(4-(4-chloroanilino)piperidin-1-yl)sulfonyl]-2-furyl)methyl]benzamide
- 4-chloro-N-({5-[(4-[4-(trifluoromethyl)anilino]piperidin-1-yl)sulfonyl]-2-furyl)methyl}benzamide
- 15 4-chloro-N-({5-[(4-{4-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]-2-furyl)methyl}benzamide
- N-({5-[(4-[4-(aminocarbonyl)anilino]piperidin-1-yl)sulfonyl]-2-furyl)methyl}-4-chlorobenzamide
- 4-chloro-N-({5-[(4-[4-(1,3-dithiolan-2-yl)anilino]piperidin-1-yl)sulfonyl]-2-furyl)methyl}benzamide
- 20 N-({5-[(4-{3-[amino(imino)methyl]anilino}piperidin-1-yl)sulfonyl]-2-furyl)methyl}-4-chlorobenzamide
- 4-chloro-N-({5-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]-2-furyl)methyl}benzamide
- 25 N-({5-[(4-anilinopiperidin-1-yl)sulfonyl]-2-furyl)methyl}-4-chlorobenzamide
- 4-nitro-N-({5-[(4-{3-[(trifluoromethyl)sulfanyl]anilino}piperidin-1-yl)sulfonyl]-2-furyl)methyl}benzamide
- 4-chloro-N-({5-[(3-{3-[(trifluoromethyl)sulfonyl]anilino}pyrrolidin-1-yl)sulfonyl]thien-2-yl)methyl}benzamide
- 30 4-chloro-N-({5-[(4-{3-[(trifluoromethyl)sulfonyl]anilino}azepan-1-yl)sulfonyl]thien-2-yl)methyl}benzamide



12. A sulfonamide derivative according to claim 11, which is selected from the group consisting of
- 4-chloro-N-[(5-{[4-(2,4-difluorobenzoyl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 5 4-chloro-N-[(5-{[4-(phenylacetyl)-1,4-diazepan-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- N-({5-[(4-anilinopiperidin-1-yl)sulfonyl]thien-2-yl}methyl)-4-chlorobenzamide
- N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide
- 10 N-[(5-{[4-(1H-benzimidazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-4-chlorobenzamide
- 4-chloro-N-{[5-({4-[3-propylanilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}benzamide
- 4-chloro-N-[(5-{[4-(4-chloroanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 15 4-chloro-N-({5-[(4-{3-[(2-hydroxyethyl)sulfonyl]anilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)benzamide
- N-{[5-({4-[3-(aminosulfonyl)anilino]piperidin-1-yl}sulfonyl)thien-2-yl]methyl}-4-chlorobenzamide
- 20 4-chloro-N-[(5-{[4-(1-naphthoyl)piperazin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- 4-nitro-N-[(5-{[4-(3-methoxyanilino)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]benzamide
- methyl 3-{[1-({5-[(4-nitrobenzoyl)amino]methyl}thien-2-yl)sulfonyl]piperidin-4-yl}amino}benzoate
- 25 N-[(5-{[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]sulfonyl}thien-2-yl)methyl]-2-hydroxybenzamide
- N-({5-[(4-{2-nitroanilino}piperidin-1-yl)sulfonyl]thien-2-yl}methyl)-3-methoxybenzamide
- 30 13. Use of a sulfonamide derivative according to formula I



I

wherein Ar¹ and Ar² are independently from each other substituted or unsubstituted aryl or heteroaryl groups;

X is O or S, preferably O;

5 R¹ is hydrogen or a C₁-C₆-alkyl group, or R¹ forms a substituted or unsubstituted 5-6-membered saturated or unsaturated ring with Ar¹;

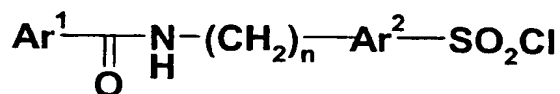
n is an integer from 0 to 5, preferably between 1-3 and most preferred 1;

Y within formula I is an unsubstituted or a substituted 4-12-membered saturated cyclic or bicyclic alkyl containing at least one nitrogen atom, whereby one nitrogen atom within said ring is forming a bond with the sulfonyl group of formula I thus providing a sulfonamide,

for the preparation of a pharmaceutical composition for the modulation of the JNK pathway.

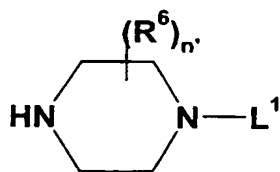
14. Use according to claim 13 for the treatment or prevention of disorders associated with the abnormal expression or activity of JNK.
15. Use according to claim 14 for the treatment or prevention of disorders associated with abnormal expression or activity of JNK2 and/or 3.
16. Use of sulfonamides according to formula I in particular according to any of claims 13 to 15 for the treatment of neuronal disorders including epilepsy; Alzheimer's disease, Huntington's disease, Parkinson's disease; retinal diseases, spinal cord injury, head trauma.
17. Use of sulfonamides according to formula I in particular according to any of claims 13 to 15 for the treatment of autoimmune diseases including Multiple Sclerosis, inflammatory bowel disease (IBD), rheumatoid arthritis, asthma, septic shock, transplant rejection.

18. Use of sulfonamides according to formula I in particular according to any of claims 13 to 15 for the treatment of cancer including breast-, colorectal-, pancreatic cancer.
19. Use of sulfonamides according to formula I in particular according to any of claims 13 to 15 for the treatment of cardiovascular diseases including stroke, arterosclerosis, myocordial infarction, myocordial reperfusion injury.
20. A pharmaceutical composition containing at least one sulfonamide derivative according to any of the claims 2 to 12 and a pharmaceutically acceptable carrier, diluent or excipient thereof.
21. Process for the preparation of a sulfonamide derivative according to any of claims 1 to 12, wherein a sulfonyl chloride V



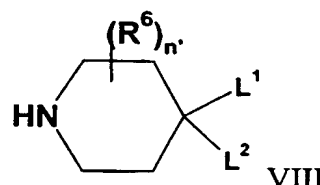
V

is reacted with an amine VII or VIII



VII

or



VIII

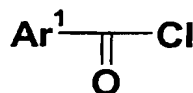
whereby $(\text{R}^6)_n$, L^1 and L^2 are as above defined.

22. A process according to claim 21, wherein a sulfonyl chloride V is obtainable by a) coupling an amine of formula II:



II

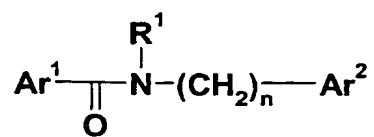
where Ar^2 and R^1 are as defined above, with an acyl chloride of formula III:



III

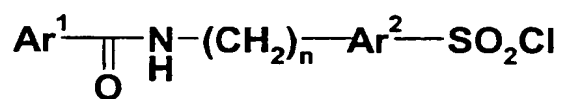
where Ar^1 is as defined above, to provide an amide of formula IV:





IV

b) sulfonating the amide of formula IV to provide a sulfonyl chloride V



V

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 00/01380

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D409/12 C07D333/34 C07D333/36 C07D413/12 C07D495/04
C07D471/04 C07D409/14 C07D405/12 A61K31/496 A61K31/445
/(C07D495/04, 333:00, 221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, WPI Data, BEILSTEIN Data, EPO-Internal, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 30992 A (BRISTOL-MYERS SQUIBB CO.;USA) 28 August 1997 (1997-08-28) cited in the application see general formula and provisos in application	1-22
A	WO 97 45403 A (PHARMACIA & UPJOHN COMPANY;USA) 4 December 1997 (1997-12-04) see whole application	1-22



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

10 November 2000

Date of mailing of the international search report

20. 11. 00

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Scruton-Evans, I



INTERNATIONAL SEARCH REPORT

Interr. Application No

PC 00/01380

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>KELLY J ET AL: "Synthesis of isomeric 3-piperidinyl and 3-pyrrolidinyl benzo[5,6]cyclohepta[1,2-b]pyridines: sulfonamido derivatives as inhibitors of Ras prenylation"</p> <p>BIOORG. MED. CHEM. (BMECEP,09680896);1998; VOL.6 (6); PP.673-686, XP000881133</p> <p>Schering-Plough Research Institute;Kenilworth; 07033; NJ; USA (US)</p> <p>the whole document</p>	1-22
A	<p>WO 98 53814 A (MERCK & CO., INC.;USA)</p> <p>3 December 1998 (1998-12-03)</p> <p>cited in the application</p> <p>the whole document</p>	1-22
A	<p>WO 99 16751 A (MERCK PATENT G.M.B.H.;GERMANY)</p> <p>8 April 1999 (1999-04-08)</p> <p>the whole document</p>	1-22
A	<p>WO 99 21859 A (GLAXO GROUP LTD ;GLENNON KIMBERLY CAROLINE (US); PEEL MICHAEL ROBE)</p> <p>6 May 1999 (1999-05-06)</p> <p>the whole document</p>	1-22
A	<p>WO 96 30017 A (SCHERING CORP)</p> <p>3 October 1996 (1996-10-03)</p> <p>cited in the application</p> <p>the whole document</p>	1-22

INTERNATIONAL SEARCH REPORT

Int. application No.
IB 00/01380

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-10,13-22(partly)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.



2

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-10,13-22(partly)

Present claims 1-10,13-22 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of the examples and closely related homologous compounds, i.e. wherein Ar1 is substituted phenyl, X is O and Ar2 is 2,5-thienyl or 2,5-furyl.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.



INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/00/01380

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9730992 A	28-08-1997	AU 718676 B AU 2136697 A BG 102738 A BR 9707614 A CN 1214685 A CZ 9802696 A EP 0892797 A HU 9902016 A JP 2000502356 T LT 98120 A, B LV 12150 A LV 12150 B NO 983892 A PL 328868 A US 6011029 A ZA 9701621 A	20-04-2000 10-09-1997 30-09-1999 27-07-1999 21-04-1999 13-10-1999 27-01-1999 28-09-1999 29-02-2000 25-06-1999 20-10-1998 20-12-1998 25-08-1998 01-03-1999 04-01-2000 25-08-1998
WO 9745403 A	04-12-1997	AU 720414 B AU 3060197 A CN 1217711 A CZ 9803701 A EP 0923542 A FI 982572 A NO 985599 A PL 330207 A	01-06-2000 05-01-1998 26-05-1999 12-05-1999 23-06-1999 27-11-1998 30-11-1998 26-04-1999
WO 9853814 A	03-12-1998	EP 1001764 A	24-05-2000
WO 9916751 A	08-04-1999	DE 19743435 A AU 9540798 A BR 9812699 A EP 1025086 A NO 20001687 A ZA 9808937 A	08-04-1999 23-04-1999 22-08-2000 09-08-2000 31-03-2000 31-03-1999
WO 9921859 A	06-05-1999	AU 1151099 A	17-05-1999
WO 9630017 A	03-10-1996	US 5684013 A AU 708244 B AU 5307296 A CA 2216291 A EP 0814807 A HU 9801396 A JP 3001982 B JP 10505102 T US 5703090 A US 5958939 A	04-11-1997 29-07-1999 16-10-1996 03-10-1996 07-01-1998 28-05-1999 24-01-2000 19-05-1998 30-12-1997 28-09-1999



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 403/06, A61K 31/55	A1	(11) International Publication Number: WO 97/30992 (43) International Publication Date: 28 August 1997 (28.08.97)
(21) International Application Number: PCT/US97/02920 (22) International Filing Date: 24 February 1997 (24.02.97) (30) Priority Data: 60/012,265 26 February 1996 (26.02.96) US 60/022,805 25 July 1996 (25.07.96) US (71) Applicant: BRISTOL-MYERS SQUIBB COMPANY [US/US]; P.O. Box 4000, Princeton, NJ 08543-4000 (US). (72) Inventors: DING, Charles, Z.; 40 Marion Drive, Plainsboro, NJ 08536 (US). HUNT, John, T.; 7 Skyfield Drive, Princeton, NJ 08540 (US). KIM, Soong-Hoon; 39-05 Ravens Crest Drive, Plainsboro, NJ 08536 (US). MITT, Toomis; 1312 Aspen Drive, Plainsboro, NJ 08536 (US). BHIDE, Rajeev; 156 Barnsbury Road, Langhorne, PA 19047 (US). LEFTHERIS, Katerina; 92 Richmond Drive, Skillman, NJ 08559 (US). (74) Agents: HOFFMAN, Frank, P. et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, NJ 08543-4000 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: INHIBITORS OF FARNESYL PROTEIN TRANSFERASE (57) Abstract This invention relates to compounds that inhibit farnesyl-protein transferase and ras protein farnesylation, thereby making them useful as anti-cancer agents. The compounds are also useful in the treatment of diseases, other than cancer, associated with signal transduction pathways operating through ras and those associated with proteins other than ras that are also post-translationally modified by the enzyme farnesyl protein transferase. The compounds may also act as inhibitors of other prenyl transferases, and thus be effective in the treatment of diseases associated with other prenyl modifications of proteins.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

INHIBITORS OF FARNESYL PROTEIN TRANSFERASE

Field of the Invention

5
This invention relates to compounds that inhibit farnesyl-protein transferase and ras protein farnesylation, thereby making them useful as anti-cancer agents. The compounds are also useful in the treatment of diseases, other than cancer, associated with signal transduction pathways
10 operating through ras and those associated with proteins other than ras that are also post-translationally modified by the enzyme farnesyl protein transferase. The compounds may also act as inhibitors of other prenyl transferases, and thus be effective in the treatment of diseases associated with other prenyl modifications of proteins.

Background of the Invention

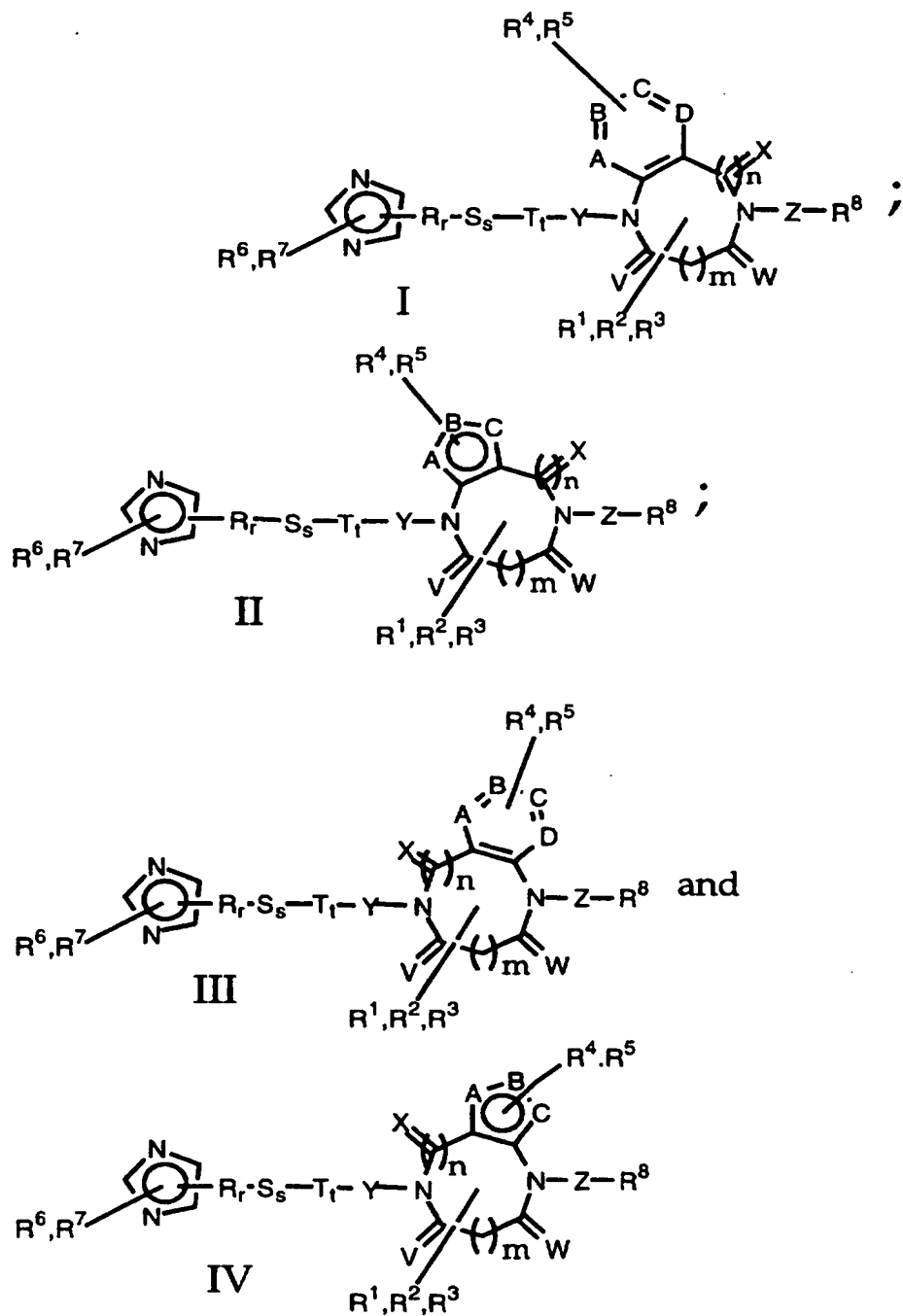
15
The mammalian ras gene family comprises three genes, H-ras, K-ras and N-ras. The ras proteins are a family of GTP-binding and hydrolyzing
20 proteins that regulate cell growth and differentiation. Overproduction of normal ras proteins or mutations that inhibit their GTPase activity can lead to uncontrolled cell division.

The transforming activity of ras is dependent on localization of the protein to plasma membranes. This membrane binding occurs via a series
25 of post-translational modifications of the cytosolic Ras proteins. The first and mandatory step in this sequence of events is the farnesylation of these proteins. The reaction is catalyzed by the enzyme farnesyl protein transferase (FPT), and farnesyl pyrophosphate (FPP) serves as the farnesyl group donor in this reaction. The ras C-terminus contains a sequence motif
30 termed a "Cys-Aaa₁-Aaa₂-Xaa" box (CAAX box), wherein Cys is cysteine, Aaa is an aliphatic amino acid, and Xaa is a serine or methionine. Farnesylation occurs on the cysteinyl residue of the CAAX box (cys-186), thereby attaching the prenyl group on the protein via a thio-ether linkage.

Brief Description of the Invention

In accordance with the present invention, compounds of the formulas I, II, III and IV

5



10

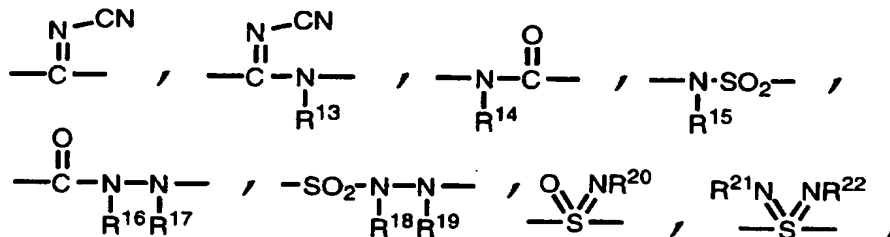
their enantiomers, diastereomers, and pharmaceutically acceptable salts, prodrugs and solvates thereof inhibit farnesyl protein transferase which is an enzyme involved in ras oncogene expression. In formulas I-IV and throughout their specification, the above symbols are defined as follows:

5 m, n, r, s and t are 0 or 1;

p is 0, 1 or 2;

V, W and X are selected from the group consisting of oxygen, hydrogen, R¹, R² or R³;

10 Z and Y are selected from the group consisting of CHR⁹, SO₂, SO₃, CO, CO₂, O, NR¹⁰, SO₂NR¹¹, CONR¹²,



or Z may be absent;

15 R⁶, R⁷, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R²⁹, R³⁰, R³¹, R³², R³³, R³⁴, R³⁵, R³⁶, R³⁷, and R³⁸ are selected from the group consisting of hydrogen, lower alkyl, substituted alkyl, aryl, or substituted aryl;

R⁴, R⁵ are selected from the group consisting of hydrogen, halo, nitro, cyano and U-R²³;

20 U is selected from the group consisting of sulfur, oxygen, NR²⁴, CO, SO, SO₂, CO₂, NR²⁵CO₂, NR²⁶CONR²⁷, NR²⁸SO₂, NR²⁹SO₂NR³⁰, SO₂NR³¹, NR³²CO, CONR³³, PO₂R³⁴ and PO₃R³⁵ or U is absent;

25 R¹, R², and R³ are selected from the group consisting of hydrogen, alkyl, alkoxy carbonyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aralkyl, cycloalkyl, aryl, substituted aryl, heterocyclo, substituted heterocyclo, cyano, carboxy, carbamyl (e.g. CONH₂) or substituted carbamyl further selected from CONH alkyl, CONH aryl, CONH aralkyl or cases where there are two substituents on the nitrogen selected from alkyl, aryl or aralkyl;

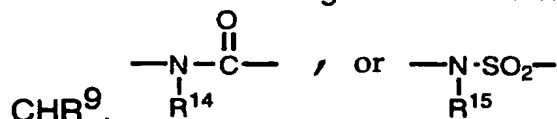
30 R⁸ and R²³ are selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aralkyl, cycloalkyl, aryl, substituted aryl, heterocyclo, substituted heterocyclo; Any two of R¹, R², and R³ can be joined to form a cycloalkyl group;

R, S and T are selected from the group consisting of CH_2 , CO and $\text{CH}(\text{CH}_2)_p\text{Q}$ wherein Q is $\text{NR}^{36}\text{R}^{37}$, OR^{38} , or CN; and

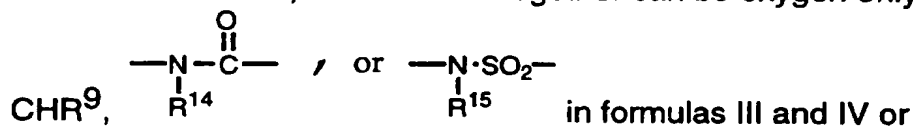
A, B, C and D are carbon, oxygen, sulfur or nitrogen.

with the provisos that

1. When m is zero then V and W are not both oxygen or
2. W and X together can be oxygen only if Z is either absent, O, NR^{10} ,

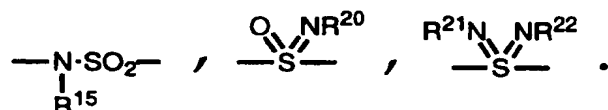


in formulas I and II, and V and X together can be oxygen only if Y is O, NR^{10} ,



3. R^{23} may be hydrogen except when U is SO, SO_2 , $\text{NR}^{25}\text{CO}_2$ or $\text{NR}^{28}\text{SO}_2$, or

4. R^8 may be hydrogen except when Z is SO_2 , CO_2 , or



- 15 Listed below are definitions of various terms used to describe this invention. These definitions apply to the terms as they are used throughout this specification, unless otherwise limited in specific instances, either individually or as part of a larger group.

- 20 The term "alkyl" refers to straight or branched chain unsubstituted hydrocarbon groups of 1 to 20 carbon atoms, preferably 1 to 7 carbon atoms. The expression "lower alkyl" refers to unsubstituted alkyl groups of 1 to 4 carbon atoms.

- 25 The term "substituted alkyl" refers to an alkyl group substituted by, for example, one to four substituents, such as, halo, trifluoromethyl, trifluoromethoxy, hydroxy, alkoxy, cycloalkoxy, heterocyclooxy, oxo, alkanoyl, aryloxy, alkanoyloxy, amino, alkylamino, arylamino, aralkylamino, cycloalkylamino, heterocycloamino, disubstituted amines in which the 2 amino substituents are selected from alkyl, aryl or aralkyl; alkanoylamino, aroylamino, aralkanoylamino, substituted alkanoylamino, substituted arylamino, substituted aralkanoylamino, thiol, alkylthio, arylthio, aralkylthio, cycloalkylthio, heterocyclothio, alkylthiono, arylthiono, aralkylthiono,
- 30

alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, sulfonamido, e.g. SO_2NH_2 , substituted sulfonamido, nitro, cyano, carboxy, carbamyl, e.g. CONH_2 , substituted carbamyl e.g. CONH alkyl, CONH aryl, CONH aralkyl or cases where there are two substituents on the nitrogen selected from alkyl, aryl or aralkyl; alkoxy carbonyl, aryl, substituted aryl, guanidino and heterocyclos, such as, indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like. Where noted above where the substituent is further substituted it will be with halogen, alkyl, alkoxy, aryl or aralkyl.

The term "halogen" or "halo" refers to fluorine, chlorine, bromine and iodine.

The term "aryl" refers to monocyclic or bicyclic aromatic hydrocarbon groups having 6 to 12 carbon atoms in the ring portion, such as phenyl, naphthyl, biphenyl and diphenyl groups, each of which may be substituted.

The term "aralkyl" refers to an aryl group bonded directly through an alkyl group, such as benzyl.

The term "substituted aryl" refers to an aryl group substituted by, for example, one to four substituents such as alkyl, substituted alkyl, halo, trifluoromethoxy, trifluoromethyl, hydroxy, alkoxy, cycloalkyloxy, heterocycloxy, alkanoyl, alkanoyloxy, amino, alkylamino, aralkylamino, cycloalkylamino, heterocycloamino, dialkylamino, alkanoylamino, thiol, alkylthio, cycloalkylthio, heterocyclothio, ureido, nitro, cyano, carboxy, carboxyalkyl, carbamyl, alkoxy carbonyl, alkylthiono, arylthiono, alkylsulfonyl, sulfonamido, aryloxy and the like. The substituent may be further substituted by halo, hydroxy, alkyl, alkoxy, aryl, substituted aryl, substituted alkyl or aralkyl.

The term "alkenyl" refers to straight or branched chain hydrocarbon groups of 2 to 20 carbon atoms, preferably 2 to 15 carbon atoms, and most preferably 2 to 8 carbon atoms, having one to four double bonds.

The term "substituted alkenyl" refers to an alkenyl group substituted by, for example, one to two substituents, such as, halo, hydroxy, alkoxy, alkanoyl, alkanoyloxy, amino, alkylamino, dialkylamino, alkanoylamino, thiol, alkylthio, alkylthiono, alkylsulfonyl, sulfonamido, nitro, cyano, carboxy, carbamyl, substituted carbamyl, guanidino and heterocyclo, e.g. indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like.

The term "alkynyl" refers to straight or branched chain hydrocarbon groups of 2 to 20 carbon atoms, preferably 2 to 15 carbon atoms, and most preferably 2 to 8 carbon atoms, having one to four triple bonds.

5 The term "substituted alkynyl" refers to an alkynyl group substituted by, for example, a substituent, such as, halo, hydroxy, alkoxy, alkanoyl, alkanoyloxy, amino, alkylamino, dialkylamino, alkanoylamino, thiol, alkylthio, alkylthiono, alkylsulfonyl, sulfonamido, nitro, cyano, carboxy, carbamyl, substituted carbamyl, guanidino and heterocyclo, e.g. imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like.

10 The term "cycloalkyl" refers to a optionally substituted, saturated cyclic hydrocarbon ring systems, preferably containing 1 to 3 rings and 3 to 7 carbons per ring which may be further fused with an unsaturated C₃-C₇ carbocyclic ring. Exemplary groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl, cyclododecyl, and
15 adamantyl. Exemplary substituents include one or more alkyl groups as described above, or one or more groups described above as alkyl substituents.

The terms "heterocycle", "heterocyclic" and "heterocyclo" refer to an optionally substituted, fully saturated or unsaturated, aromatic or
20 nonaromatic cyclic group, for example, which is a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic ring system, which has at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2, 3, or 4 heteroatoms selected from nitrogen atoms, oxygen
25 atoms and sulfur atoms, where the nitrogen and sulfur heteroatoms may also optionally be oxidized and the nitrogen heteroatoms may also optionally be quaternized. The heterocyclic group may be attached at any heteroatom or carbon atom.

Exemplary monocyclic heterocyclic groups include pyrrolidinyl, pyrrolyl, indolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, oxazolyl, oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolyl, thiadiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxazepinyl, azepinyl, 4-piperidonyl,
35 pyridyl, N-oxo-pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, tetrahydrothiopyranyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, tetrahydrothiopyranylsulfone, thiamorpholinyl

sulfone, 1,3-dioxolane and tetrahydro-1, 1-dioxothienyl, dioxanyl, isothiazolidinyl, thietanyl, thiiranyl, triazinyl, and triazolyl, and the like.

Exemplary bicyclic hetrocyclic groups include benzothiazolyl, benzoxazolyl, benzothienyl, quinuclidinyl, quinolinyl, quinolinyl-N-oxide, 5 tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuryl, chromonyl, coumarinyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl (such as furo[2,3-c]pyridinyl, furo[3,1-b]pyridinyl] or furo[2,3-b]pyridinyl), dihydroisoindolyl, dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-quinazolinyl), benzisothiazolyl, benzisoxazolyl, 10 benzodiazinyl, benzofurazanyl, benzothiopyranyl, benzotriazolyl, benzpyrazolyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, dihydrobenzopyranyl, indolinyl, isochromanyl, isoindolinyl, naphthyridinyl, phthalazinyl, piperonyl, purinyl, pyridopyridyl, quinazolinyl, 15 tetrahydroquinolinyl, thienofuryl, thienopyridyl, thienothienyl, and the like.

Exemplary substituents include one or more alkyl groups as described above or one or more groups described above as alkyl substituents.

Also included are smaller heterocyclos, such as, epoxides and aziridines.

20 The term "heteroatoms" shall include oxygen, sulfur and nitrogen.

The "ABC" ring and the "ABCD" fused ring to the diazepine ring may be monocyclic or bicyclic, e.g. naphthyl or quinolyl in nature.

The compounds of formulas I-IV may form salts which are also within the scope of this invention. Pharmaceutically acceptable (i.e. non- 25 toxic, physiologically acceptable) salts are preferred, although other salts are also useful, e.g., in isolating or purifying the compounds of this invention.

The compounds of formulas I-IV may form salts with alkali metals such as sodium, potassium and lithium, with alkaline earth metals such as calcium and magnesium, with organic bases such as dicyclohexylamine, 30 tributylamine, pyridine and amino acids such as arginine, lysine and the like. Such salts may be obtained, for example, by exchanging the carboxylic acid protons, if they contain a carboxylic acid, in compounds I-IV with the desired ion in a medium in which the salt precipitates or in an aqueous medium followed by evaporation. Other salts can be formed as known to those 35 skilled in the art.

The compounds for formulas I-IV may form salts with a variety of organic and inorganic acids. Such salts include those formed with hydrogen

chloride, hydroxy methane sulfonic acid, hydrogen bromide, methanesulfonic acid, sulfuric acid, acetic acid, trifluoroacetic acid, maleic acid, benzenesulfonic acid, toluenesulfonic acid and various others (e.g., nitrates, phosphates, borates, tartrates, citrates, succinates, benzoates, ascorbates, salicylates and the like). Such salts may be formed by reacting compounds I-IV in an equivalent amount of the acid in a medium in which the salt precipitates or in an aqueous medium followed by evaporation.

In addition, zwitterions ("inner salts") may be formed.

Compounds of the formulas I-IV may also have prodrug forms. Any compound that will be converted *in vivo* to provide the bioactive agent (i.e., the compound for formulas I-IV) is a prodrug within the scope and spirit of the invention.

For example compounds of the formulas I-IV may be a carboxylate ester moiety. The carboxylate ester may be conveniently formed by esterifying any of the carboxylic acid functionalities found on the disclosed ring structure(s).

Various forms of prodrugs are well known in the art. For examples of such prodrug derivatives, see:

- a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol.42, p. 309-396, edited by K. Widder, et al. (Academic Press, 1985);
- b) A Textbook of Drug Design and Development, edited by Krosgaard-Larsen and H. Bundgaard, Chapter 5, "Design and Application of Prodrugs," by H. Bundgaard, p. 113-191 (1991);
- c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);
- d) H. Bundgaard, et al., Journal of Pharmaceutical Sciences, 77, 285 (1988); and
- e) N. Kakeya, et al., Chem Phar Bull, 32, 692 (1984).

It should further be understood that solvates (e.g., hydrates) of the compounds of formulas I-IV are also within the scope of the present invention. Methods of solvation are generally known in the art.

Preferred Moieties

For compounds of the present invention, the following moieties are preferred:

Compounds of Formulas I, II, III and IV wherein m is zero.

5 More preferred are compounds of Formula I, II, III and IV wherein m is zero and n is one.

Most preferred are compounds of formula I wherein m, r, s and t are zero, n is one and "ABCD" is a carbocyclic ring, e.g., benzo.

Use and Utility

10 The compounds of formulas I-IV are inhibitors of S-farnesyl protein transferase. They are thus useful in the treatment of a variety of cancers, including (but not limited to) the following;

- carcinoma, including that of the bladder, breast, colon, kidney, liver, 15 lung, including small cell lung cancer, ovary, prostate, testes, pancreas, esophagus, stomach, gall bladder, cervix, thyroid and skin, including squamous cell carcinoma;
- hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell 20 lymphoma, T-cell lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma, and Burketts lymphoma;
- hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia;
- 25 - tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma, and schwannomas;
- tumors of mesenchymal origin, including fibrosarcoma, rhabdomyosarcoma, and osteosarcoma;
- other tumors, including melanoma, xenoderma pigmentosum, 30 keratoactanthoma, seminoma, thyroid follicular cancer and teratocarcinoma.

The compounds of formulas I-IV are especially useful in treatment of tumors having a high incidence of ras involvement, such as colon, lung, and pancreatic tumors and in tumors in which a prenyl transferase contributes to tumor maintenance, tumor growth or tumor development. By 35 the administration of a composition having one (or a combination) of the compounds of this invention, development of tumors in a mammalian host is reduced, or tumor burden is reduced, or tumor regression is produced.

Compounds of formulas I-IV may also inhibit tumor angiogenesis, thereby affecting the growth of tumors. Such anti-angiogenesis properties of the compounds of formulas I-IV may also be useful in the treatment of certain forms of blindness related to retinal vascularization.

5 Compounds of formulas I-IV may also be useful in the treatment of diseases other than cancer that may be associated with signal transduction pathways operating through ras, e.g., neurofibromatosis, atherosclerosis, pulmonary fibrosis, arthritis, psoriasis, glomerulonephritis, restenosis following angioplasty or vascular surgery, hypertrophic scar formation,
10 polycystic kidney disease and endotoxic shock. Compounds I-IV may be useful as anti-fungal agents.

 Compounds of formula I-IV may induce or inhibit apoptosis, a physiological cell death process critical for normal development and homeostasis. Alterations of apoptotic pathways contribute to the
15 pathogenesis of a variety of human diseases. Compounds of formula I-IV, as modulators of apoptosis, will be useful in the treatment of a variety of human diseases with aberrations in apoptosis including cancer (particularly, but not limited to follicular lymphomas, carcinomas with p53 mutations, hormone dependent tumors of the breast, prostate and ovary, and precancerous
20 lesions such as familial adenomatous polyposis), viral infections (including but not limited to herpesvirus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus), autoimmune diseases (including but not limited to systemic lupus erythematosus, immune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel diseases and autoimmune diabetes mellitus), neurodegenerative disorders (including but not limited to
25 Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, spinal muscular atrophy and cerebellar degeneration), AIDS, myelodysplastic syndromes, aplastic anemia, ischemic injury associated myocardial infarctions, stroke and
30 reperfusion injury, arrhythmia, atherosclerosis, toxin-induced or alcohol induced liver diseases, hematological diseases (including but not limited to chronic anemia and aplastic anemia), degenerative diseases of the musculoskeletal system (including but not limited to osteoporosis and arthritis), aspirin-sensitive rhinosinusitis, cystic fibrosis, multiple sclerosis,
35 kidney diseases, and cancer pain.

 Compounds of formulas I-IV may also be useful in the treatment of diseases associated with farnesyl transferase substrates other than ras (e.g.,

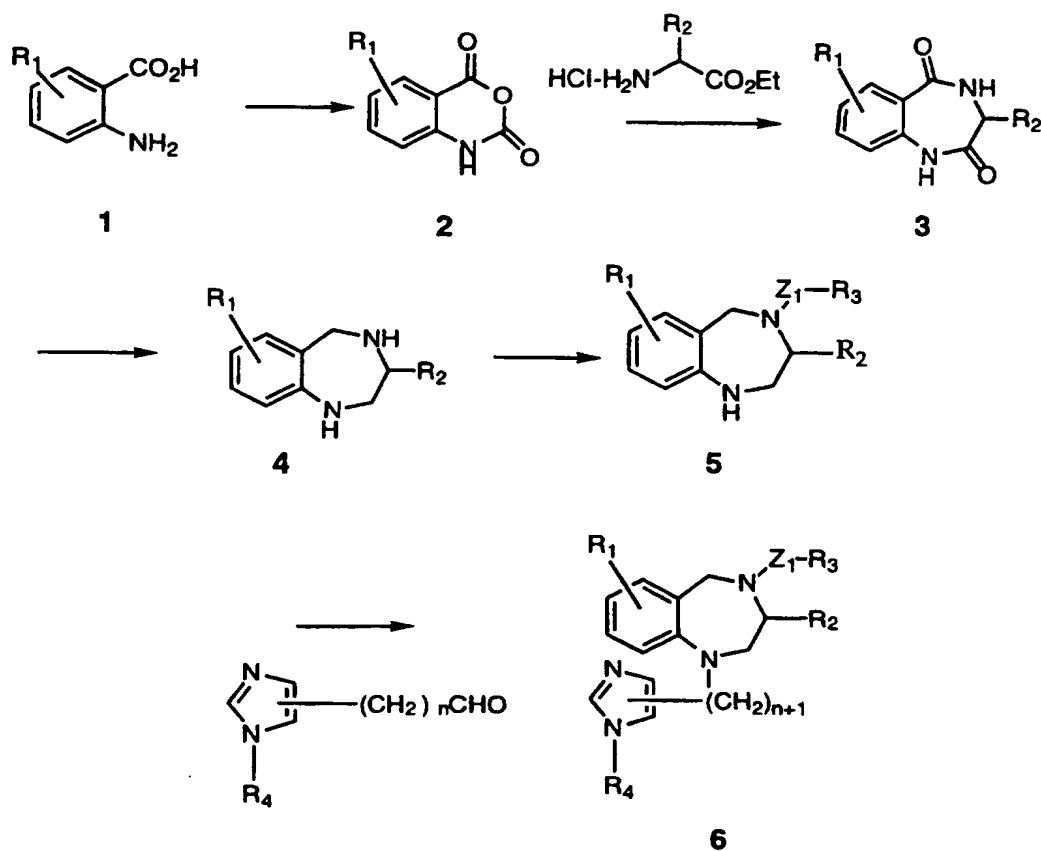
nuclear lamins, transducin, rhodopsin kinase, cGMP phosphodiesterase, TC21, phosphorylase kinase, Rap2, RhoB, RhoE, PRL1) that are also post-translationally modified by the enzyme farnesyl protein transferase.

Compounds of formulas I-IV may also act as inhibitors of other prenyl transferases (e.g., geranylgeranyl transferase I and II), and thus be effective in the treatment of diseases associated with other prenyl modifications (e.g., geranylgeranylation) of proteins (e.g. the rap, rab, rac and rho gene products and the like). For example, they may find use as drugs against Hepatitis delta virus (HDV) infections, as suggested by the recent finding that geranylgeranylation of the large isoform of the delta antigen of HDV is a requirement for productive viral infection [J. S. Glen, et al., Science, 256, 1331 (1992)].

The compounds of this invention may also be useful in combination with known anti-cancer and cytotoxic agents and treatments, including radiation. If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent within its approved dosage range. Compounds of formulas I-IV may be used sequentially with known anticancer or cytotoxic agents and treatment, including radiation when a combination formulation is inappropriate.

Farnesyl transferase assays were performed as described in V. Manne et al., Drug Development Research, 34, 121-137, (1995). The compounds of Examples 1-431 inhibited farnesyl transferase with IC 50 values between 0.1nM and 100uM.

The compounds of this invention may be formulated with a pharmaceutical vehicle or diluent for oral, intravenous, intraperitoneal, subcutaneous, intraabdominal, intramuscular, rectal, vaginal or topical administration. Oral administration may involve the use of slow release formulations, such as biodegradable polymers or prodrugs. The pharmaceutical composition can be formulated in a classical manner using solid or liquid vehicles, diluents and additives appropriate to the desired mode of administration. Orally, the compounds can be administered in the form of tablets, capsules, granules, powders and the like. The compounds may be administered in a dosage range of about 0.05 to 200 mg/kg/day, preferably less than 100 mg/kg/day, in a single dose or in 2 to 4 divided doses.

Process of Preparation**Scheme 1**

5

$$Z_1 = \text{CO}, \text{SO}_2, \text{CO}_2, \text{CONR}_5, \text{SO}_3, \text{SO}_2\text{NR}_5, \text{C}(\text{NCN})\text{NR}_5$$
Step 1

The first step is accomplished by the reaction of the anthranilic acid with a phosgene equivalent, such as, phosgene or triphosgene in a mixed aqueous/organic solvent at room temperature to 50°C range.

Step 2

The product is reacted with an amino acid hydrochloride salt or an amino acid ester hydrochloride salt in pyridine at an elevated temperature with reflux as preferred. Step 2 of Scheme 1 may be performed in 2 steps, wherein the isatoic anhydride is condensed with an amino acid in an organic solvent solvent such as pyridine at from 0°C to reflux and the resulting anthraniloylamino acid is cyclized under standard amide bond forming

conditions, e.g., using HOBt/carbodiimide in an organic solvent such as DMF at from 0°C to room temperature. Some compounds 1 of Scheme 1 wherein R₁ = halogen are not commercially available. Such compounds 3, 4 or 5 of Scheme 1 wherein R₁ = halogen can be prepared from compounds 3, 4 or 5 of Scheme 1 wherein R₁ = hydrogen by halogenation, for example by reaction with bromine in an organic solvent such as acetic acid at from 0°C to room temperature. The compound 3 wherein R₁ is aryl or heteroaryl can be prepared from the compound 3 wherein R₁ is bromo, iodo or trifluoromethanesulfonyloxy by a palladium coupling of an aryl or heteroaryl metalloid derivative such as phenylboronic acid in a mixed aqueous/organic solvent, e.g. THF/DMF/water, in the presence of a base, e.g. sodium carbonate, at from room temperature to 90°C. (Alternatively, the compound of Scheme 1 where R₁ = aryl or heteroaryl is also prepared from a compound 2 of Scheme 5 where R₁ is bromo, iodo or trifluoromethanesulfonyloxy by reaction with an aryl metalloid derivative such as phenylboronic acid or tributyl-stannylpyridine in a deoxygenated organic (e.g., THF) or mixed aqueous/organic solvent system such as aqueous NaHCO₃/toluene in the presence of a palladium catalyst such as tetrakis(triphenylphosphine) palladium at from room temperature to 100°C. Deprotection then affords the target compound.) Alternatively such Suzuki or Stille couplings can be performed on a compound 1 of Scheme 1, or on a compound 4 of Scheme 1, or on a compound 5 of Scheme 1 where the unacylated benzodiazepine nitrogen may be optionally protected, e.g., with a trifluoroacetyl group, and subsequently deprotected. The compound 3 wherein R₁ is alkoxy is prepared by alkylation of the corresponding hydroxy compound under standard conditions. The compound 3 wherein R₁ is alkylaminoalkylaryl is prepared from the compound 3 wherein R₁ is an aryl aldehyde by reductive amination under standard conditions.

30 **Step 3**

Thereafter the compound 3 is reacted with a reducing agent, such as lithium aluminum hydride or borane in an inert organic solvent, such as, tetrahydro-furan at from room temperature to reflux. If R₁ or R₂ contain functional groups, e.g., CO₂R, which are reduced by, e.g. lithium aluminum hydride, to, e.g. CH₂OH, these groups will also be reduced by step 3. The compound 4 or 6 wherein R₁ is CN can be prepared from the compound 4 or 6 wherein R₁ = halogen by displacement with CuCN in an inert solvent such

as NMP at elevated temperature. The compound 4 wherein R₁ is CO₂H can be prepared from the compound 4 wherein R₁ = CN by hydrolysis, e.g. by heating with aqueous sodium hydroxide in a suitable solvent such as ethanol at 100°C; thereafter the product wherein R₁ = CONR₅R₆ may be prepared by standard amide bond coupling conditions.

Step 4

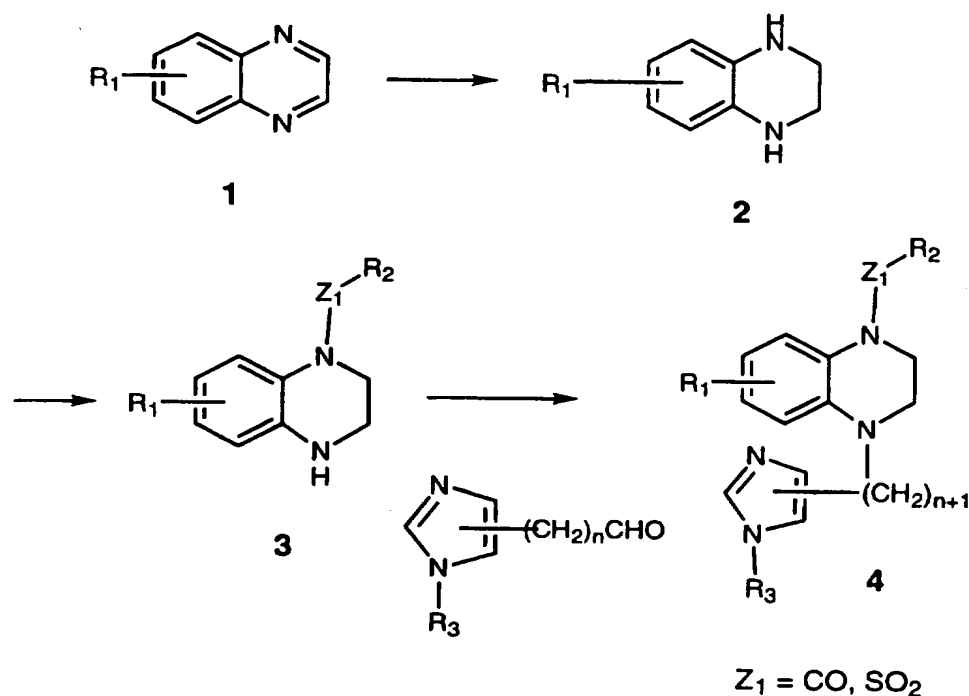
Thereafter the product is acylated or sulfonylated under standard conditions at from -78°C to room temperature (e.g., by reaction with an acid halide R₃COX wherein X is Cl or Br in an inert organic solvent, e.g. acetonitrile, or in a mixed aqueous/organic solvent e.g. NaOH/dichloroethane; by reaction with an O-phenyl ester in an inert organic solvent, e.g. acetonitrile; by reaction with a carboxylic acid in the presence of a coupling agent, e.g. DCC or EDC in an inert organic solvent, such as DMF; by reaction with a haloformate such as ethyl, isopropyl or 4-nitrophenylchloroformate in an inert solvent such as dichloromethane at from 0°C to room temperature in the presence of an optional base such as diisopropylethylamine to form carbamates, some of which, e.g. 4-nitrophenyl-carbamate, are reacted with an amine, e.g. N,N,N'-trimethylethylenediamine, at from room temperature to 110°C to form ureas; by reaction with a carboxylic or sulfonyl anhydride such as succinic anhydride or trifluoromethanesulfonyl anhydride in an inert solvent such as ethyl acetate, dichloromethane or pyridine at from 0°C to room temperature in the presence of an optional base such as diisopropylethylamine; by reaction with an isocyanate in an inert solvent such as THF; by reaction with a carbamyl chloride R₅R₆NCOX wherein X is Cl or Br in an inert solvent such as acetonitrile in the presence of a base such as diisopropylethylamine/dimethyl-aminopyridine; by reaction with a sulfonyl halide R₃SO₂X wherein X is Cl or Br in a mixed aqueous/organic solvent e.g. NaOH/CH₂Cl₂; by reaction with a halosulfonate ROSO₂X wherein X is Cl or Br in an inert solvent such as CH₂Cl₂; by reaction with a sulfamoyl chloride R₅R₆NSO₂X wherein X is Cl or Br in an inert solvent such as acetonitrile in the presence of a base such as diisopropylethylamine/dimethyl-aminopyridine; by reaction with an N-cyanothiourea NH(CN)C(S)NR₅R₆ in the presence of a coupling reagent such as a carbodiimide in an inert solvent such as DMF at about room temperature; by reaction with a cyanocarbonimidate such as diphenylcyanocarbonimidate

in a suitable solvent such as DMF in the presence of a base such as diisopropylethylamine at from room temperature to 80°C, followed by reaction with an amine such as methylamine at about room temperature). The compound 5 wherein R₁ is halogen, e.g. bromine, may be prepared from the compound 5 wherein R₁ = H by reaction with a halogenating agent, e.g. tetrabutylammonium perbromide, in an inert solvent such as chloroform at about room temperature. Where R₁ or R₂ contain CH₂OH, the acylation may be performed in such a manner as to obtain the diamide ester; the ester may then be cleaved, e.g., by sodium methoxide in methanol and the resulting alcohol oxidized to an acid, e.g., by Jones reagent; the N₁ amide may then be cleaved, e.g., by KOH in aqueous methanol at reflux, and the acid may be coupled with amines under standard peptide coupling conditions to form compounds 5 of Scheme 1 where R₁ or R₂ is a carboxamide. Where R₁ or R₂ contain CH₂O-Prot, the protecting group may be removed, e.g., Boc by treatment with an acid such as TFA in an inert solvent such as dichloromethane to form a compound 5 or 6 where R₁ or R₂ is CH₂OH. The compound 5 where R₁ or R₂ is aryloxyalkyl is prepared from a compound 5 where R₁ or R₂ is CH₂OH by transformation of the alcohol into a leaving group such as a triflate. e.g., by treatment with triflic anhydride in dichloromethane at -40°C, and displacement with an alkoxide salt, e.g., in dichloromethane at from -40°C to room temperature. The compound 5 where R₁ or R₂ is CH₂NH₂ is prepared from a compound 5 where R₁ or R₂ is CH₂OH by transformation of the alcohol into a leaving group such as a triflate. e.g., by treatment with triflic anhydride in dichloromethane at -40°C, and displacement with ammonia, e.g., in dichloromethane at from -40°C to room temperature. The amine may be subsequently coupled to carboxylic acids by standard amide bond coupling conditions. Where the compound 5 is sulfonylated with a beta-haloalkylsulfonyl halide, the halide may then be eliminated by a base such as diisopropylethylamine and then nucleophiles such as dimethylamine or sodium imidazolate may be added to the resulting unsaturated sulfonamide by treatment in an organic solvent such as THF or dichloromethane at from room temperature to reflux. Where the compound 5 is acylated or sulfonylated with an acylating or sulfonylating agent which contains a leaving group, e.g. chloride or bromide, that leaving group may be displaced by nucleophiles, e.g., by amines such as dimethylamine or N-methylpiperazine in an inert solvent such as THF or DMF in the presence of an optional base such as diisopropylethylamine at from 0°C to 110°C.

Step 5

Thereafter the various products can undergo reductive alkylation in the presence of an acid e.g. acetic acid, a reducing agent e.g. $\text{NaBH}(\text{OAc})_3$ in an inert organic solvent e.g. dichloroethane at about room temperature. Reductive alkylation may also be performed using hydrogen and a catalyst such as Pd on carbon in a solvent such as ethanol in the presence of an acid such as acetic acid at about room temperature.

Thereafter, the compound of Scheme 1 where R_1 = halogen can be metallated and quenched, e.g., with water to form the compound where R_1 = H or with carbon dioxide to form the compound where R_1 = CO_2H ; this acid may be coupled with amines under standard peptide coupling conditions to form compounds of Scheme 1 where R_1 is a carboxamide. The compound of Scheme 1 wherein R_1 = halogen can be metallated and quenched with a ketone such as cyclohexanone followed by reduction of the alcohol with for example trifluoroacetic acid/sodium borohydride to form the compound where R_1 = e.g., cyclohexyl. The compound of Scheme 1 in which the imidazole contains a 2-dimethylaminomethyl group can be prepared by standard Mannich conditions. The compound of Scheme 1 in which R_1 = OH can be prepared from the compound of Scheme 1 in which R_1 = OMe by dealkylation, e.g., by treatment with BBr_3 . The compound of Scheme 1 in which R_1 = arylOalkyl can be prepared from the compound of Scheme 1 in which R_1 = HOalkyl by Mitsunobu reaction with the aryl alcohol. The compound of Scheme 1 in which R_3 = aryl- NH_2 or heteroaryl- NH_2 can be prepared from the compound of Scheme 1 in which R_3 = aryl- NO_2 or heteroaryl- NO_2 by reduction (e.g., SnCl_2) under standard conditions. The product can be further acylated, sulfonylated or reductively aminated under standard conditions.

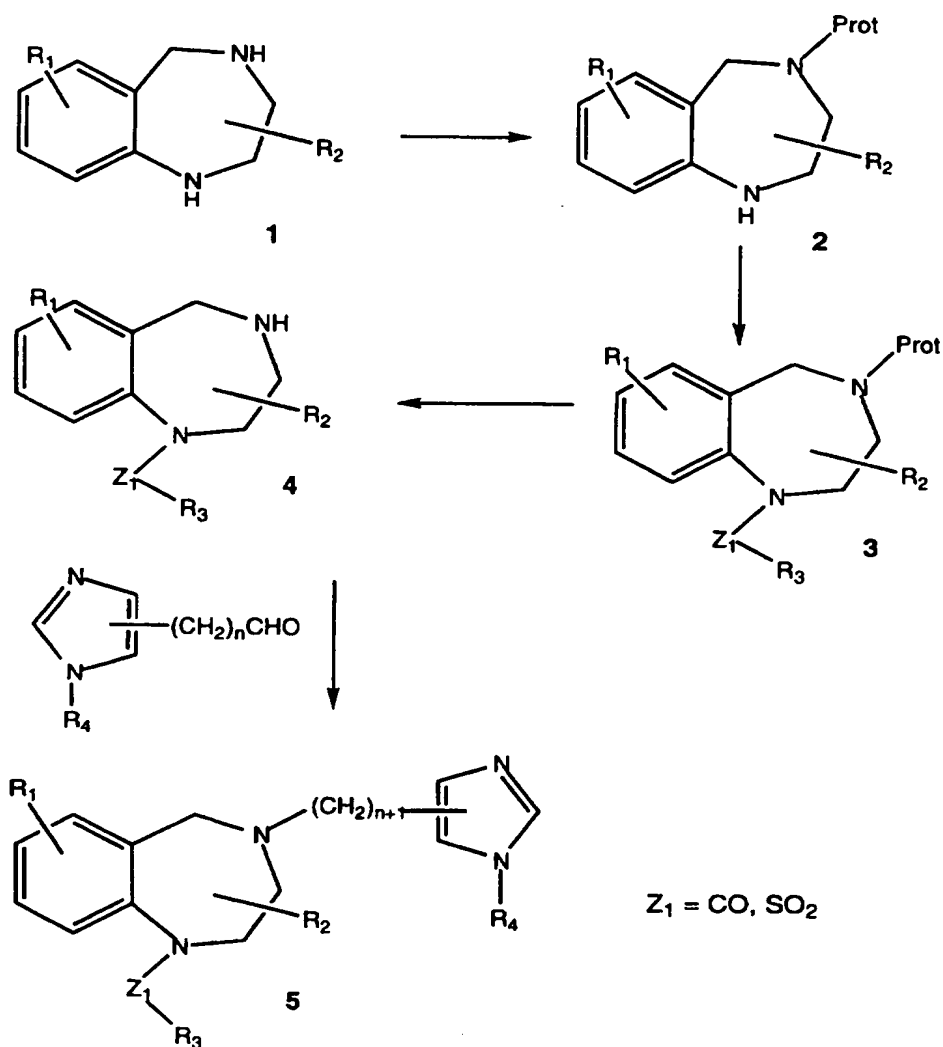
Scheme 2Step 1

In Scheme 2 the starting material is reduced via hydrogenation in the presence of platinum oxide. The reaction is carried out in the presence of an alcohol e.g. ethanol at about room temperature.

Step 2 and 3

Thereafter the product is monoacylated or monosulfonylated under standard conditions at from $-78^\circ C$ to room temperature (e.g., by reaction with an acid halide R_2COX wherein X is Cl or Br in an inert organic solvent, e.g. acetonitrile, or in a mixed aqueous/organic solvent e.g. $NaOH$ /methylene chloride; or by reaction with a sulfonyl halide R_3SO_2X wherein X is Cl or Br in an organic solvent e.g. CH_2Cl_2 in the presence of a base such as triethylamine). Thereafter the product undergoes a reductive alkylation as outlined in the last step of Scheme 1.

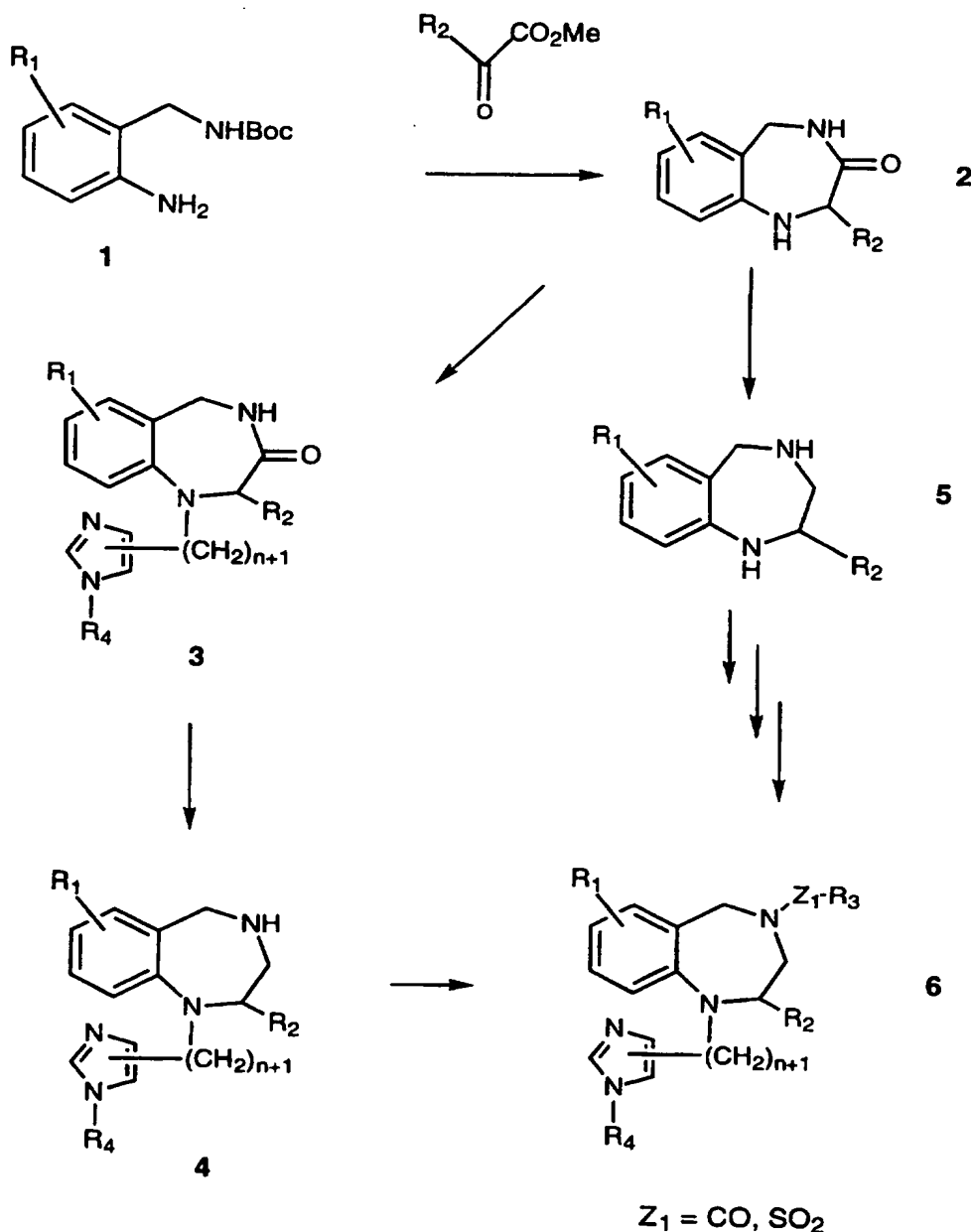
Scheme 3



- In Scheme 3, compound 1 is suitably protected by, for example, a tertbutoxycarbonyl group. The reaction is carried out in an inert organic solvent e.g. THF at about room temperature. The compound 2 where R₁ is an amine may be selectively acylated, e.g., by reaction with isobutylchloroformate in an inert solvent such as methylene chloride in the presence of a base such as diisopropylethylamine at about room temperature. The compound 2 where an R₁ is R₅CONH and another R₁ is Br is prepared from the compound where an R₁ is R₅CONH by bromination, e.g. with tetrabutylammonium tribromide in an inert solvent such as chloroform at about room temperature. Thereafter the compound 2 is reacted with a compound of the formula R₃COCl in the presence of pyridine

in an inert organic solvent, such as, dichloroethane at from about 0°C to room temperature. Thereafter the compound 3 is deprotected by reaction with, for exampl , trifluoroacetic acid in an inert organic solvent, such as, dichloroethane at about room temperature. Thereafter the compound 4

5 undergoes reductive alkylation following the steps outlined in Scheme 1.

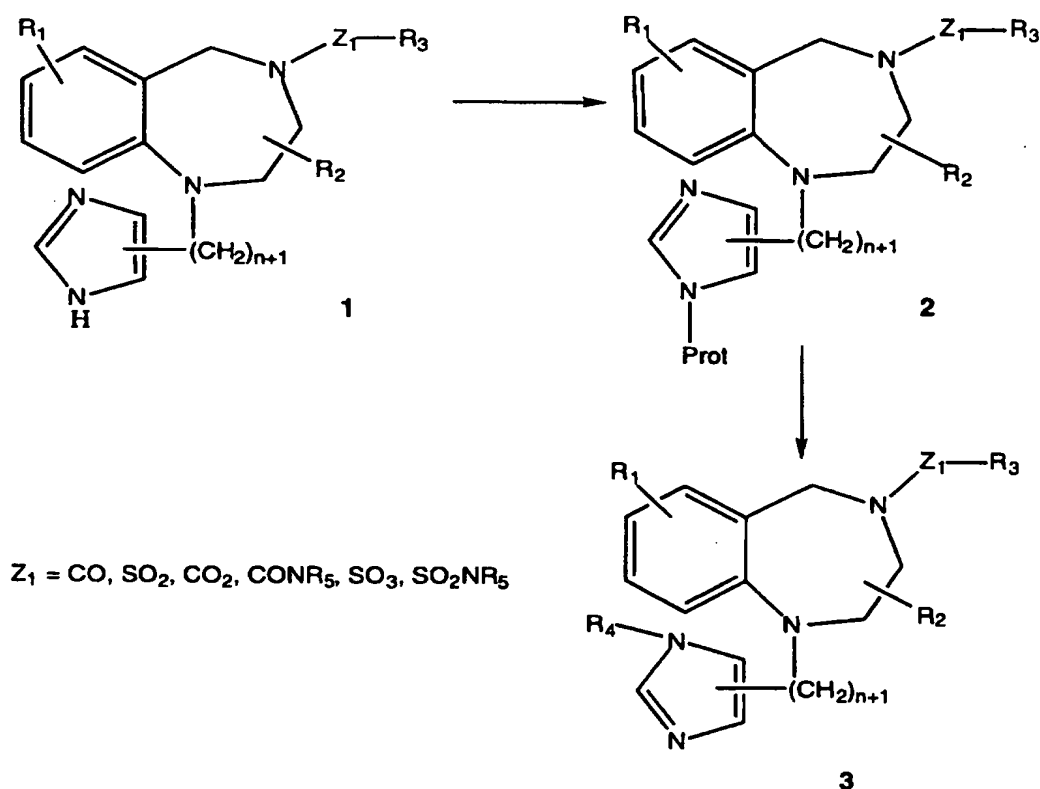
Scheme 4

In Scheme 4 the compound 1 is reacted with a compound of the formula $\text{R}_2\text{COCO}_2\text{Me}$ in the pr sence of an organic acid e.g. acetic acid, a

10 reducing agent, such as, NaCNBH_3 or $\text{NaBH}(\text{OAc})_3$ in an inert organic

- solvent, such as, dichloroethan at about room temperature. The intermediate is thereafter deprotected by reaction with, for example, trifluoroacetic acid in an inert organic solvent, e.g. CH₂Cl₂ at about room temperature, and cyclized by heating, e.g., at 60°C to form the compound 2.
- 5 Thereafter the compound 2 undergoes reductive alkylation as outlined in Scheme 1 to form a compound 3. The compound 3 may be reduced, e.g. with lithium aluminum hydride, to a compound 4, which may be reacted to form a compound 6 as described in Scheme 12. Alternatively, the compound 2 is reduced to the compound 5, as outlined in Scheme 1, and
- 10 the compound 5 is reacted as outlined in Scheme 1.

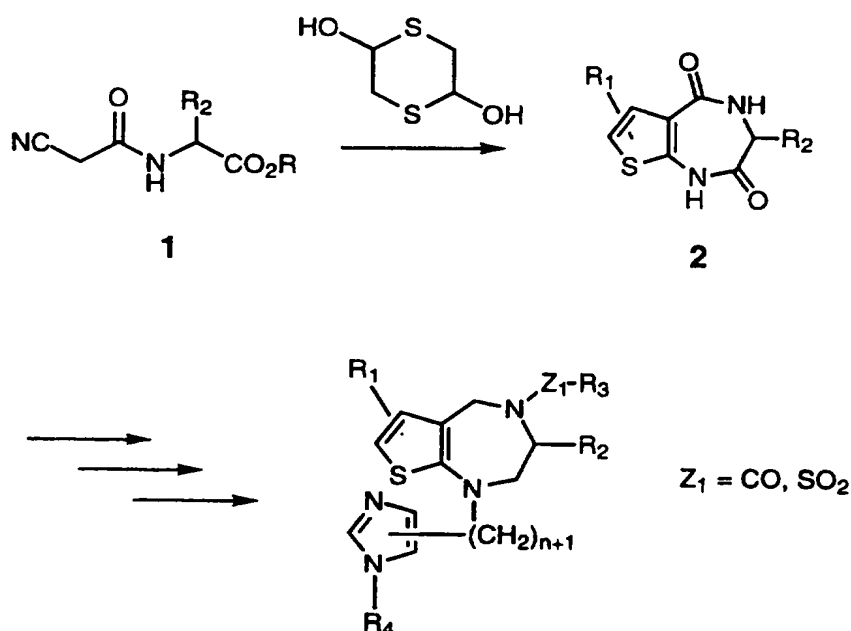
Scheme 5



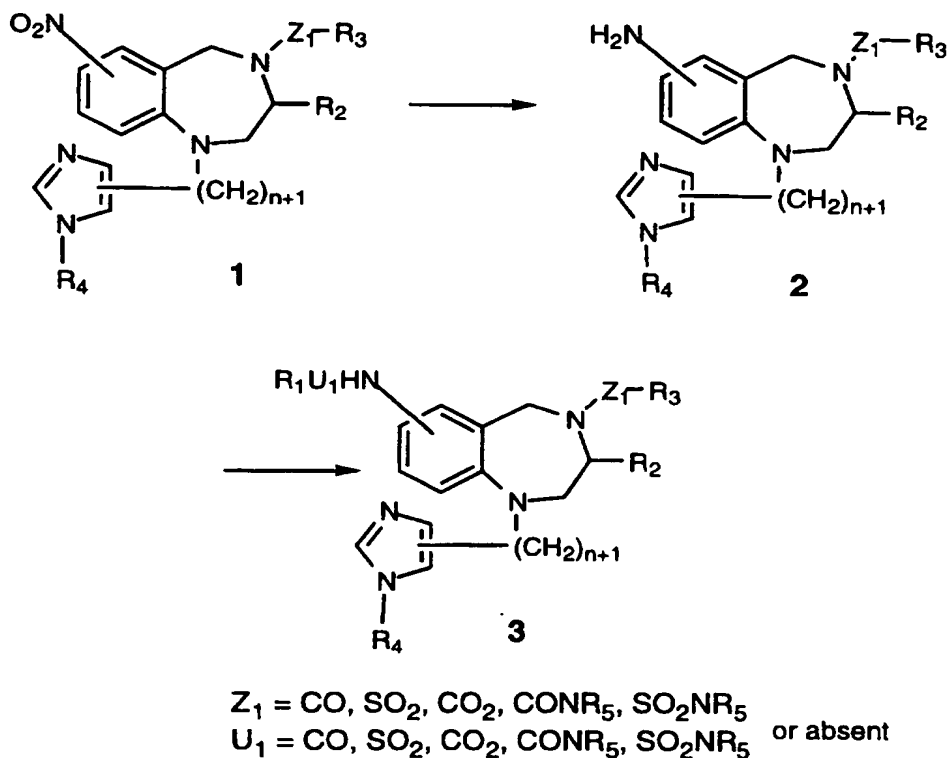
- 15 In Scheme 5 the compound 1 is protected by reaction with, for example, triphenylmethyl chloride or Boc anhydride in an inert organic solvent e.g. acetonitrile or tetrahydrofuran, from about room temperature to reflux. Thereafter the compound 2 is reacted with a compound of the formula

- R₄-L wherein L is a leaving group such as triflate, in the presence of a base such as diisopropylethylamine in an inert organic solvent such as tetrahydrofuran at from about -78°C to room temperature. R₄ may contain a protecting group, e.g., phthalimide, removable by e.g. hydrazine. The reaction of Scheme 5 with R₄-L may also be performed on a compound 1 to directly produce a compound 3 without protection/deprotection.

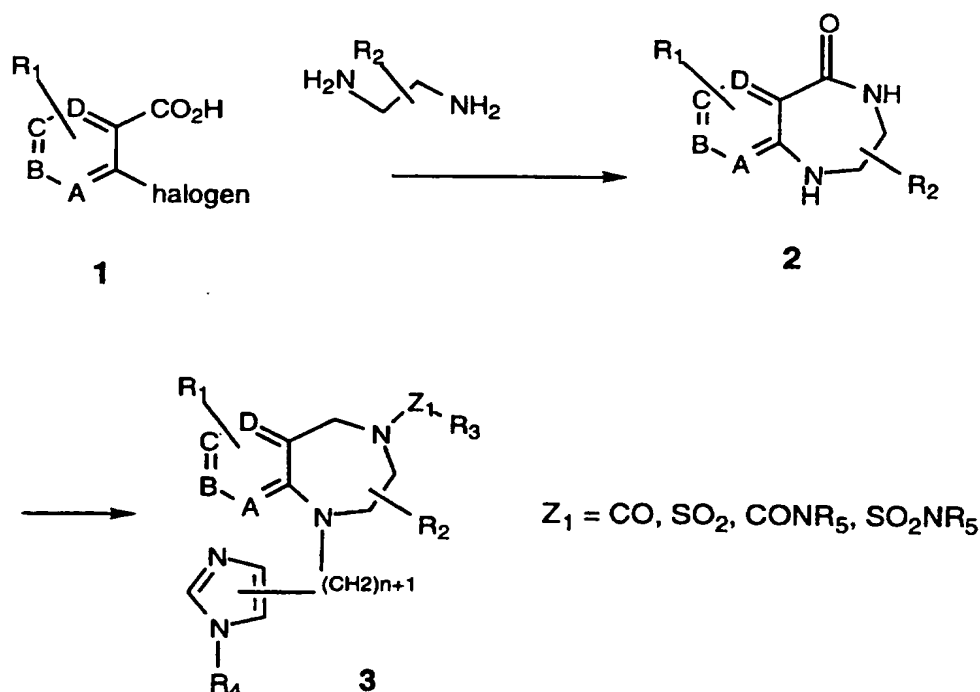
Scheme 6



- In Scheme 6, a cyanoacetyl amino acid is reacted with a dithianediol in a suitable solvent such as ethanol in the presence of bases such as piperidine and triethylamine at from room temperature to 80°C. The intermediate is then cyclized in a suitable solvent such as pyridine in the presence of a catalyst such as pyridinium hydrochloride at an elevated temperature such as 130°C. Thereafter the compound 2 is reacted as described in Scheme 1.

Scheme 7

- The compound 1 of Scheme 7 undergoes reduction (e.g., Fe, SnCl₂, or TiCl₃) under standard conditions. The compound 2 is acylated or sulfonated under standard conditions (e.g., by reaction with an anhydride and an acylation catalyst such as DMAP, by reaction with an acid halide, by reaction with a carboxylic acid under standard peptide coupling conditions, by reaction with an alkoxycarbonylchloride, by reaction with an isocyanate, by reaction with a sulfonyl halide or by reaction with a sulfamyl chloride) or reductively alkylated under standard conditions (e.g., by reaction with an aldehyde and a reducing agent such as NaCNBH₃ or Na(OAc)₃BH in an organic solvent such as dichloroethane or DMF in the presence of an acid such as acetic acid at from 0°C to room temperature).

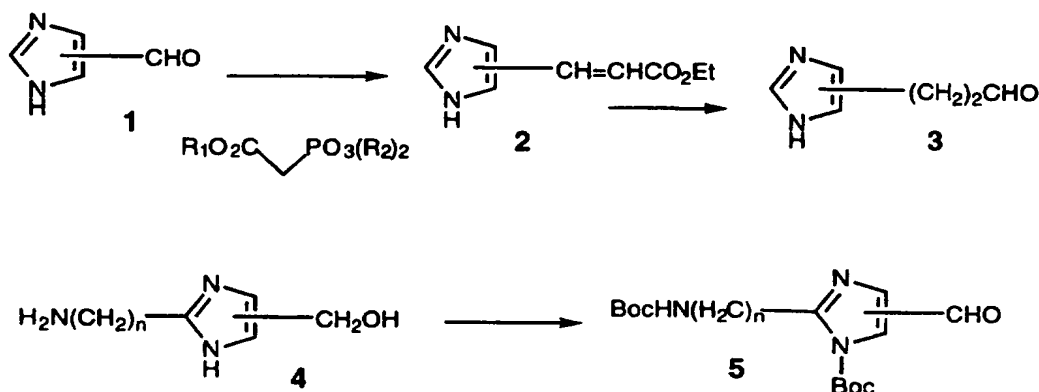
Scheme 8

- 5 The compound 1 of Scheme 8 is reacted with an ethylenediamine and the product 2 undergoes reduction, selective acylation or sulfonylation and reductive alkylation to produce a compound 3 as outlined in Scheme 1. Alternatively, Step 1 of Scheme 8 may be performed in 2 steps, wherein the ethylenediamine is condensed with the halogenated heterocycle either neat
- 10 or in an organic solvent at elevated temperature and the resulting amino acid is cyclized under standard amide bond forming conditions, e.g., using HOBt/carbodiimide in an organic solvent such as DMF or pyridine at from 0°C to room temperature. Some compounds 1 of Scheme 8 wherein R₁ =
- 15 wherein R₁ = halogen are not commercially available. Such compound 2 of Scheme 8 wherein R₁ = halogen can be prepared from compound 2 of Scheme 8 wherein R₁ = hydrogen by halogenation, for example by reaction with bromine in an organic solvent such as acetic acid at from 0°C to room temperature. The compound 2 wherein R₁ = aryl or heteroaryl can be prepared from the compound 2 wherein R₁ is halogen or
- 20 trifluoromethanesulfonyloxy by standard Suzuki or Stille couplings as described for Step 2 of Scheme 1. Thereafter the product undergoes

reduction, acylation or sulfonylation, and reductive alkylation as outlined in Scheme 1. Compound 2 of Scheme 8 may itself undergo reductive alkylation with an imidazole containing aldehyde as outlined in Scheme 1 to afford a target compound.

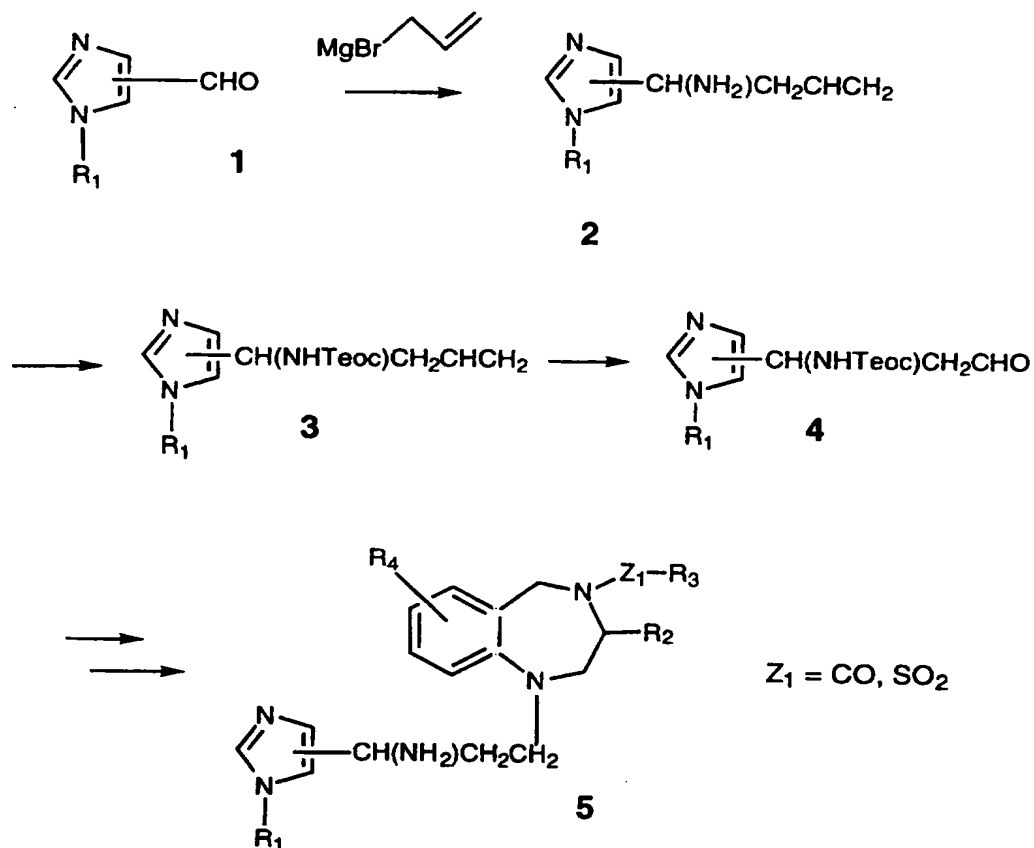
5

Scheme 9 (imidazole aldehydes)

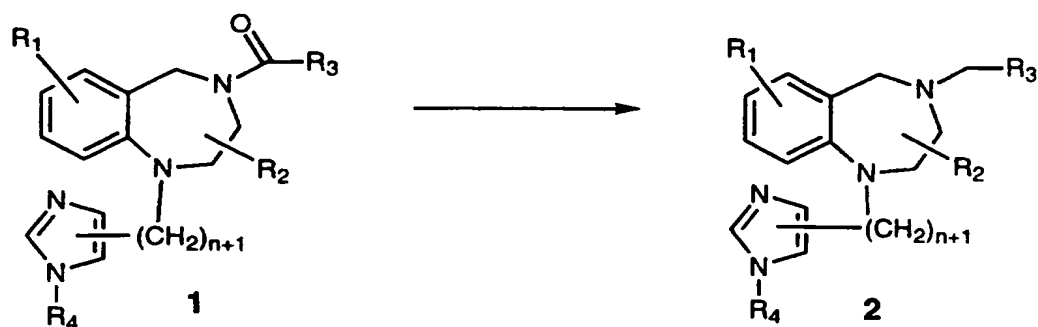


- 10 Some imidazole aldehydes are prepared as follows. An imidazole containing aldehyde undergoes a Wittig reaction with a compound of the formula triethylphosphonoacetate in the presence of a base, such as, sodium hydride in an inert organic solvent, such as dimethoxyethane, at from about 0°C to room temperature. The product is hydrogenated in an alcohol
- 15 e.g. ethanol at about room temperature and reduced by reaction with DIBAL in for example dichloroethane at about -78°C. Alternatively, some aminoalkyl containing imidazolylalkanols, prepared by known methods (e.g., Buschauer, et. al., Arch. Pharm., 315, 563, (1982)) are protected with a Boc group as in Scheme 3, step 1, and undergo an oxidation, e.g. under
- 20 Swern conditions.

Scheme 10

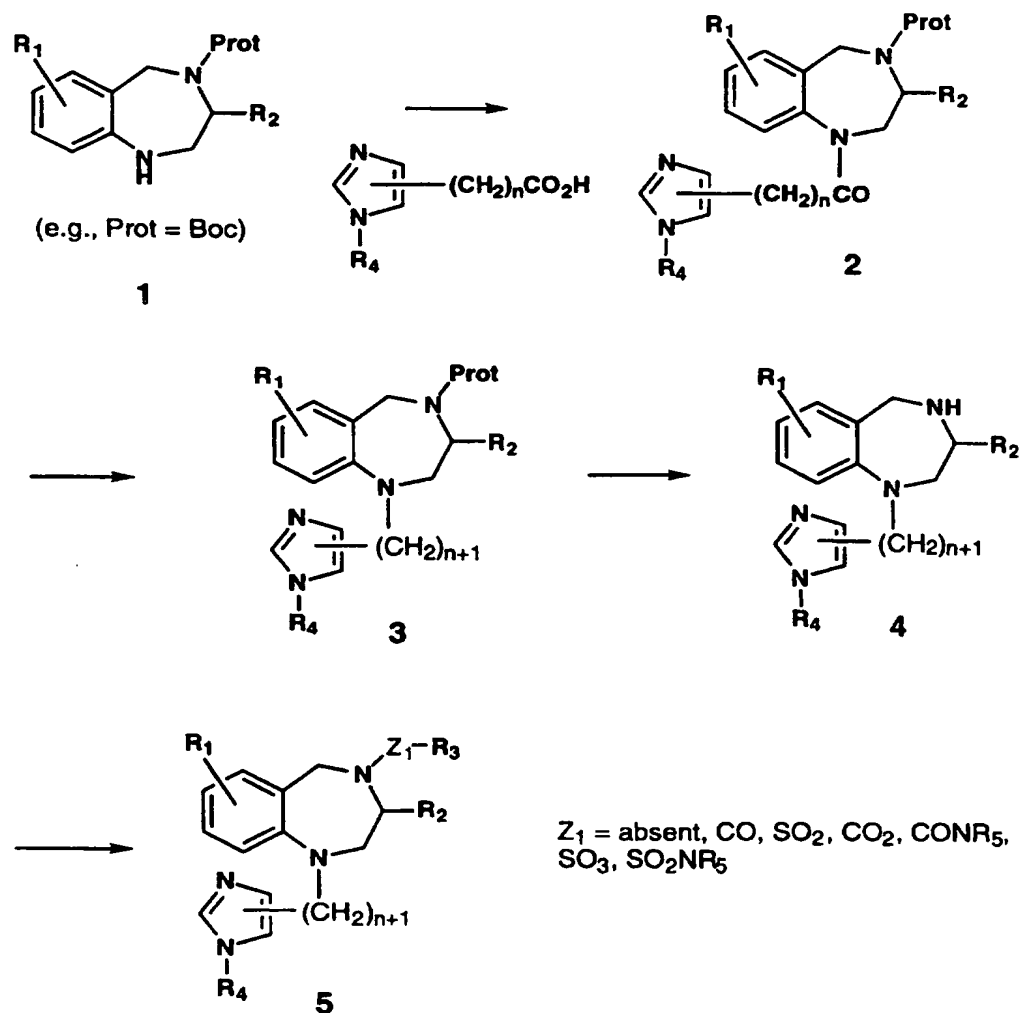


In Scheme 10 the starting material is reacted with allyl magnesium bromide in the presence of lithium hexamethyldisilazide in an inert solvent e.g. THF at from about -78 °C to room temperature. The product is protected, e.g. with a Teoc group, in an aqueous/organic solvent e.g. aqueous dioxane at about room temperature. The product is oxidized by reaction with e.g. OsO₄/NaIO₄ in aqueous dioxane at about room temperature. Thereafter the product undergoes reductive alkylation as in Scheme 1 and thereafter the product is deprotected with tetrabutylammonium fluoride at from room temperature to 50 °C in THF.

Scheme 11

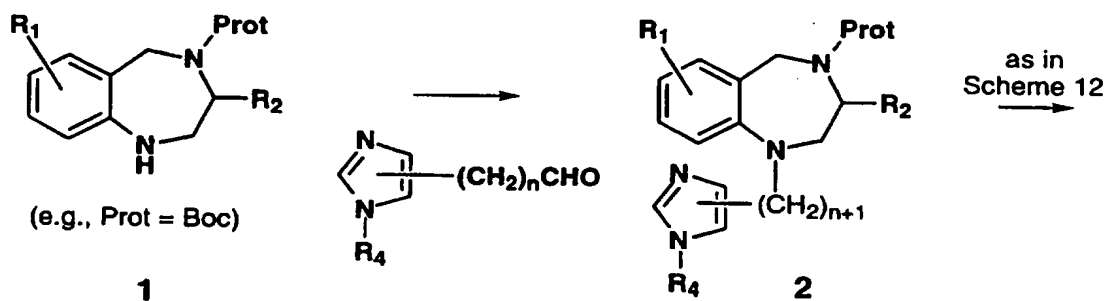
In Scheme 11 the starting material is reduced with e.g. lithium aluminum hydride in an inert organic solvent e.g. ethylene glycol dimethyl ether at from about 0°C to reflux.

5

Scheme 12

In step 1 of Scheme 12, a monoprotected benzodiazepine such as that described in Scheme 3 is coupled with an optionally protected imidazole-containing carboxylic acid using standard amide bond formation methods such as isobutylchloroformate in an organic solvent such as THF at from -30°C to room temperature. In step 2 of Scheme 12, the resulting amide is reduced with for example borane in an organic solvent such as THF at from room temperature to reflux. A compound 3 of Scheme 12 may contain a nitro group which may be reduced, e.g., by TiCl_3 , to an amine, which may then be acylated or sulfonylated as described in Scheme 7. In step 3 of Scheme 12, the amine protecting group is removed (e.g., Boc by an acid such as TFA in an organic solvent such as methylene chloride). In step 4 of Scheme 12, the resulting compound is reacted under standard conditions with a variety of active acylating or sulfonylating agents to form the claimed compound, such as acids under carbodiimide conditions or acid chlorides to form amides; carbonates or chloroformates to form carbamates; carbamyl chlorides or isocyanates to form ureas; sulfonyl chlorides to form sulfonamides; halosulfonates to form sulfamates; sulfamoyl chlorides to form sulfonylureas. In step 4 of Scheme 12, the resulting compound is alternatively reacted under standard reductive amination conditions with aldehydes as described in Step 5 of Scheme 1 to form the claimed compounds. If the imidazole is optionally protected, it is then deprotected.

Scheme 13

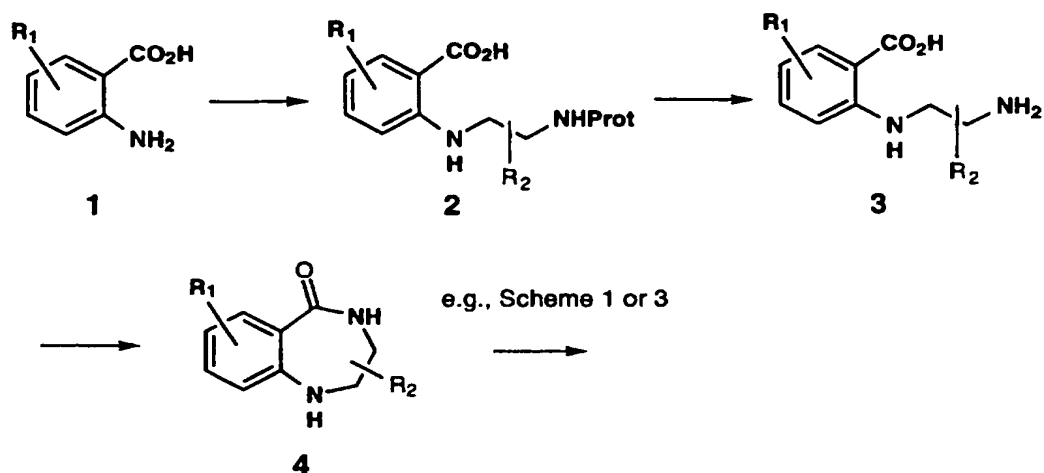


25

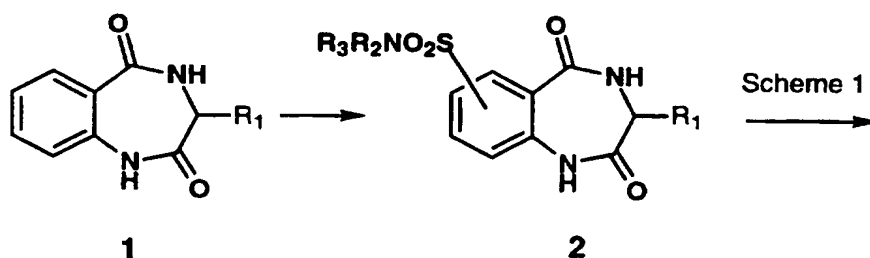
In step 1 of Scheme 13, a monoprotected benzodiazepine such as that described in Scheme 3 is reductively alkylated with an imidazole-containing aldehyde and a reducing agent such as NaCNBH_3 or $\text{Na}(\text{OAc})_3\text{BH}$ in an organic solvent such as dichloroethane or DMF in the

presence of an acid such as acetic acid at from 0°C to room temperature. Thereafter, the product is reacted as described in Scheme 12. The product 2 may be attached to a solid support, e.g. polystyrene resin, and the reactions of Scheme 1 may be performed on resin-bound material. Removal from the support, e.g. by treatment with an acid such as trifluoroacetic acid in the presence of a scavenger such as triethylsilane at about room temperature, then provides the compound 6 of Scheme 1.

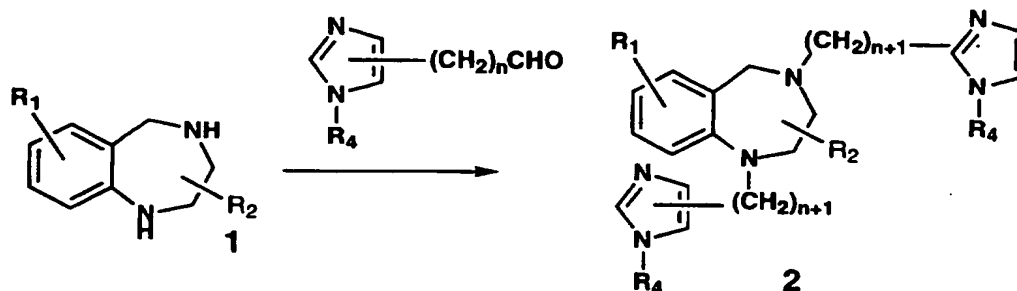
Scheme 14



In step 1 of Scheme 14, an aminobenzoic acid is reductively aminated with an N-protected aminoaldehyde under standard conditions, e.g. by reaction with a hydride reagent such as sodium triacetoxyborohydride or sodium cyanoborohydride in a suitable solvent such as methylene chloride or methanol in the presence of an acid such as acetic acid at from 0°C to about room temperature. The product is deprotected by, e.g., removal of Boc by treatment with an acid such as TFA or HCl in the presence of an optional scavenger such as dimethylsulfide in a suitable solvent such as methylene chloride or dioxane at about room temperature or removal of Fmoc by treatment with a secondary amine in tetrahydrofuran at about room temperature. Thereafter, the product is cyclized under standard amide bond forming conditions, such as by treatment with diphenylphosphoryl azide in an organic solvent such as DMF. Thereafter, the product is reacted as described in Scheme 1.

Scheme 15

In step 1 of Scheme 15, a benzodiazepinedione is sulfonated with chlorosulfonic acid and the resulting sulfonyl chloride is condensed with an amine. Thereafter, the product is reacted as described in Scheme 1.

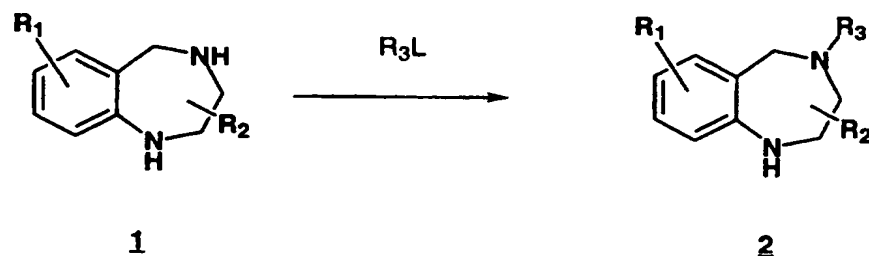
Scheme 16

10

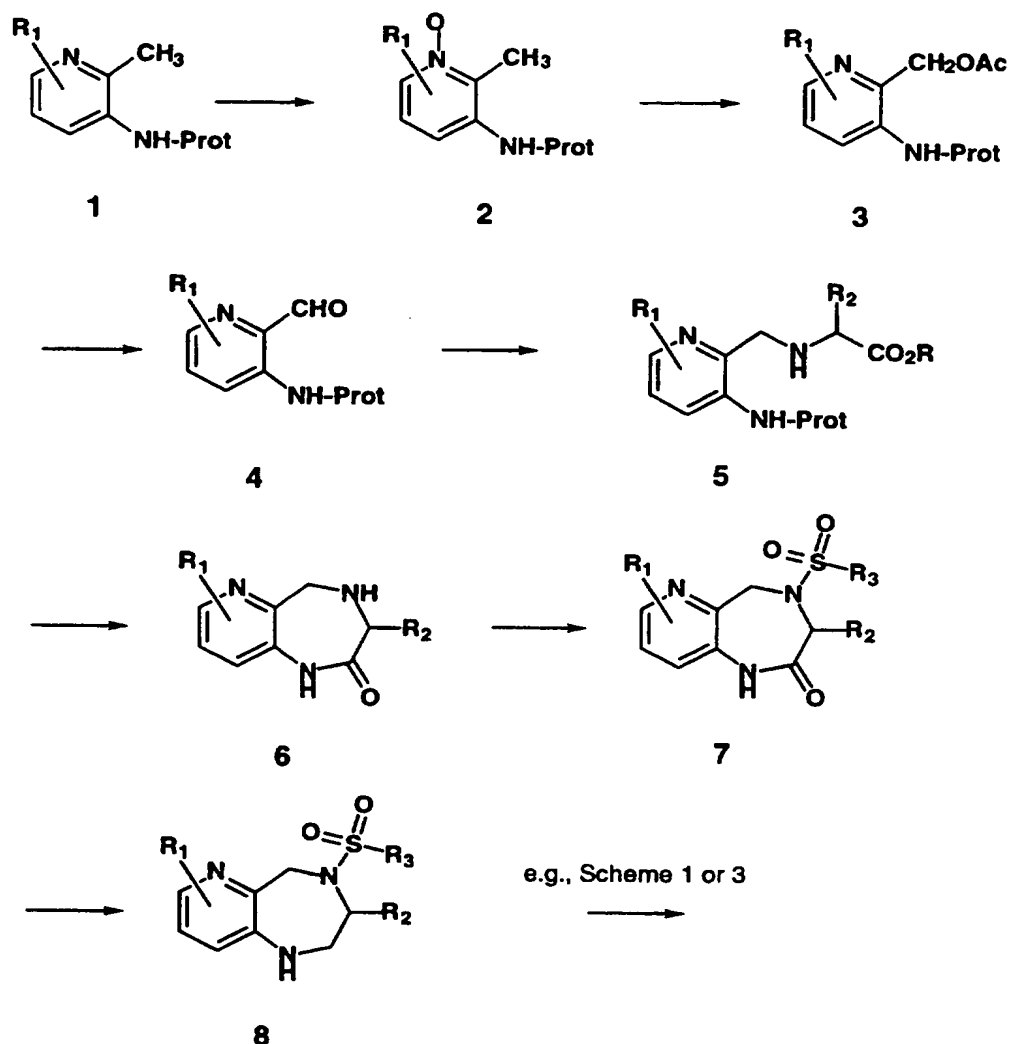
In step 1 of Scheme 16, a benzodiazepine of Scheme 1 can be doubly reductively alkylated with an imidazole containing aldehyde and a reducing agent such as NaCNBH₃ or Na(OAc)₃BH in an organic solvent such as dichloroethane or DMF in the presence of an acid such as acetic acid at from 0°C to room temperature.

15

Scheme 17



- 5 In step 1 of Scheme 17, a benzodiazepine of Scheme 1 can be reacted with R₃-L in an inert solvent such as DMF, THF or methylene chloride in the presence of a base such as diisopropylethylamine or potassium carbonate at from 0°C to 100°C, where L is a leaving group such as chloride, bromide, mesylate, tosylate or triflate and R₃ is a substituted alkyl group, a substituted aryl group or a substituted heterocyclic group. Thereafter, the product is reacted as described in Scheme 1.

Scheme 18Step 1

- 5 The first step is accomplished by the reaction of a pyridine containing a protected amino group and a methyl group with an oxidizing agent, such as hydrogen peroxide in a suitable solvent such as aqueous acetic acid or trifluoroacetic acid at from room temperature to 75°C.

10 Step 2

The product is acylated with an acylating agent such as acetic anhydride and rearranged by heating from room temperature to 90°C in a suitable solvent such as acetic acid.

Step 3

The product is deacylated, e.g., with aqueous NaOH at from room temperature to 50°C and oxidized to the aldehyde with e.g. MnO₂ in a suitable solvent such as tetrahydrofuran at about room temperature.

Step 4

The product is reductively aminated with an aminoacid ester under standard conditions, e.g., by hydrogenation in an inert solvent such as methanol or by reaction with a hydride reagent such as sodium triacetoxyborohydride in a suitable solvent such as methylene chloride/acetic acid at about room temperature.

Step 5

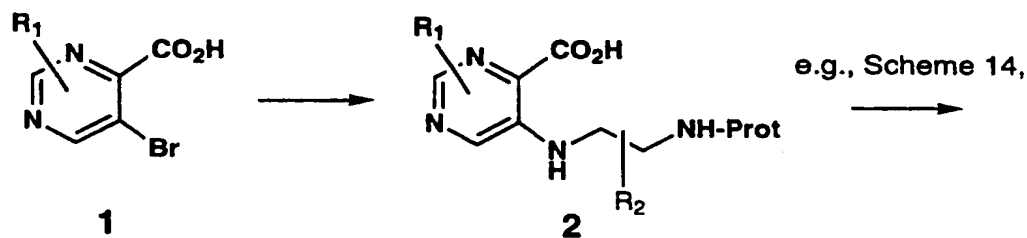
The product is deprotected and cyclized with, e.g. treatment with polyphosphoric acid at from room temperature to 100°C.

Step 6

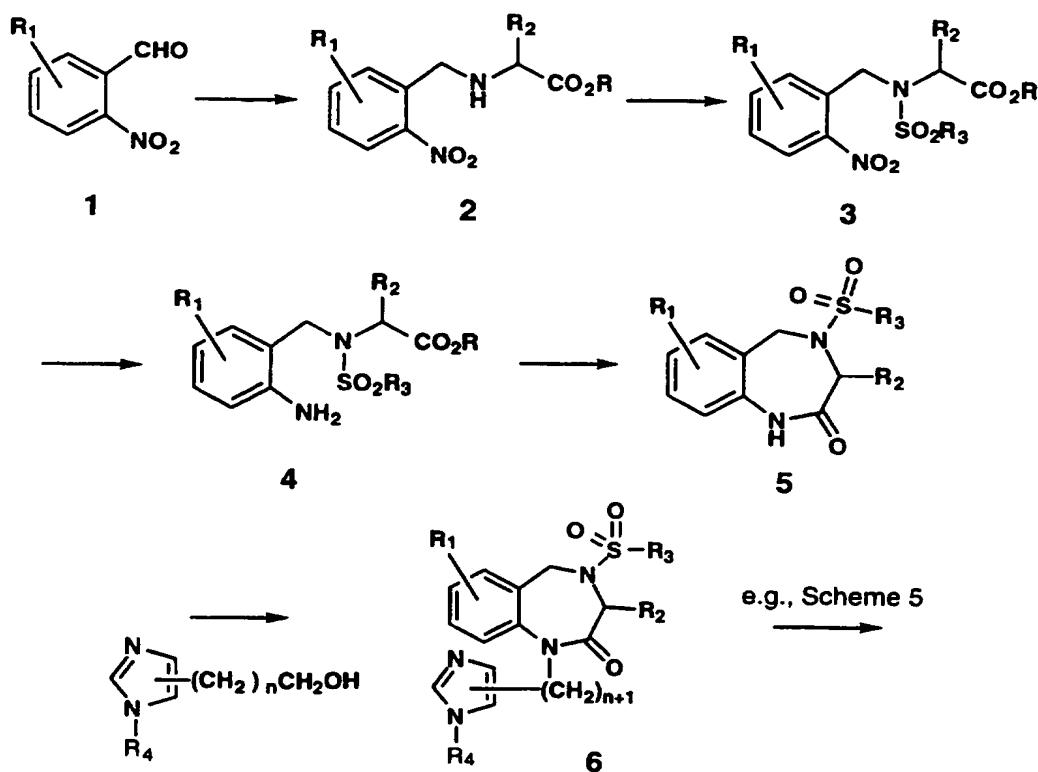
The product is sulfonylated as described for Step 4 of Scheme 1.

Step 7

The product is reduced as described for Step 3 of Scheme 1. Thereafter, the product is reacted as described in Step 5 of Scheme 1.

Scheme 19

The first step is accomplished by the reaction of a pyrimidine containing a halide and a carboxylic acid group with an optionally monoprotected diamine in a suitable solvent such as water in the presence of a catalyst such as CuSO₄ at from room temperature to 100°C. Thereafter, the product is reacted as described in Scheme 14.

Scheme 20

5

Step 1

The first step is accomplished by reductive amination of a nitrobenzaldehyde with an amino acid ester under standard conditions, e.g., by reaction with a hydride reagent such as sodium triacetoxyborohydride in a suitable solvent such as methylene chloride/acetic acid at about room temperature.

10

Step 2

The product is sulfonlated as described for Step 4 of Scheme 1.

15

Step 3

The nitro group of the product is reduced to an amine under standard conditions, such as reaction with SnCl_2 or TiCl_3 . The compound where $\text{R}_1 = \text{Br}$ may be prepared from the compound where $\text{R}_1 = \text{H}$ by bromination, such as reaction with tetrabutylammonium perbromide in an inert solvent such as chloroform at about room temperature.

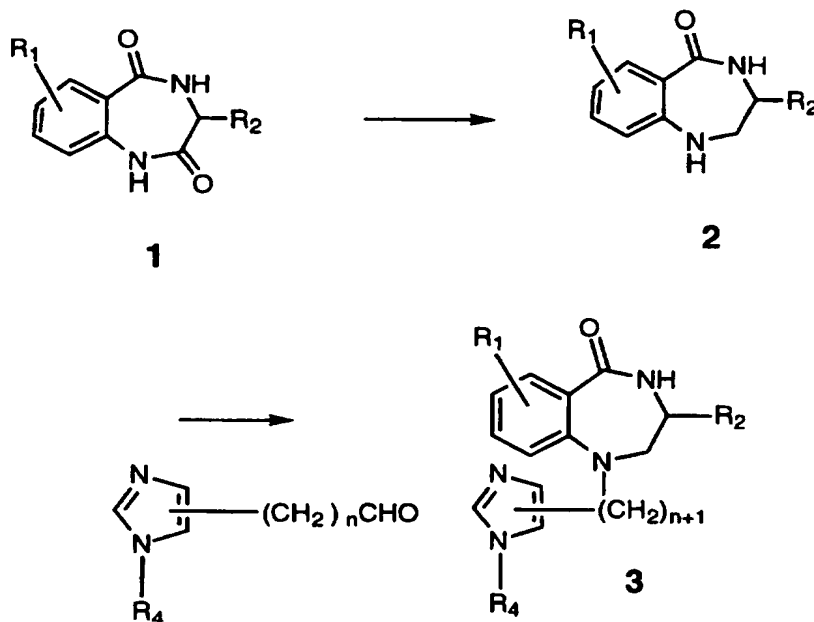
20

Step 4

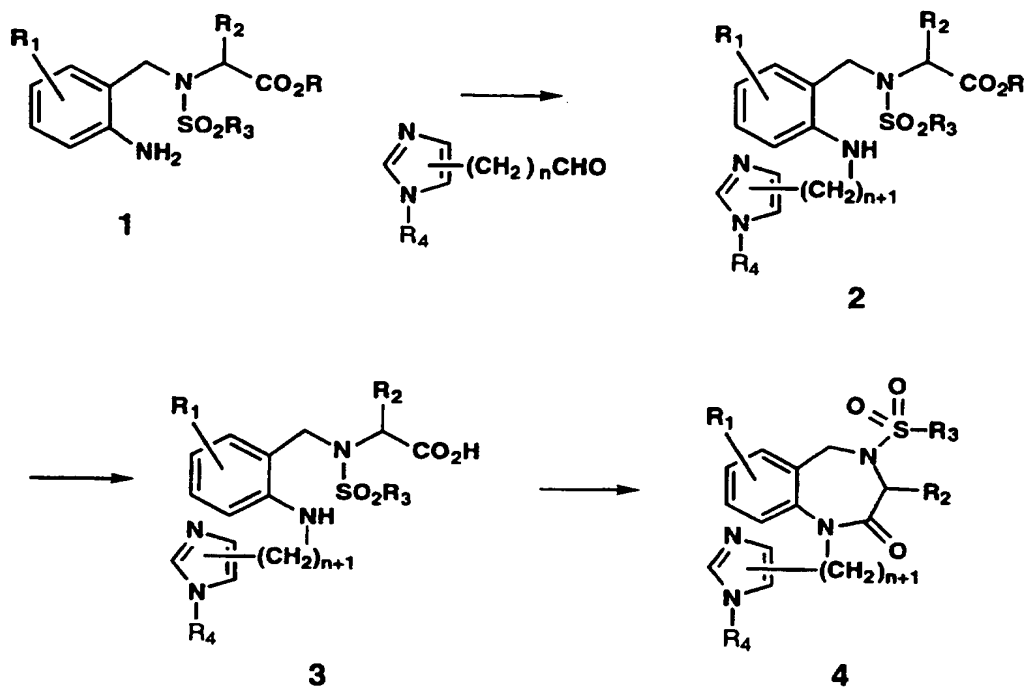
The product is cyclized by heating with CuCN in an inert solvent such as N-methylpyrrolidinone at from room temperature to 195°C. The compound where R₁ = CN is prepared from the compound where R₁ = halogen under the same conditions.

Step 5

The product is alkylated with an optionally protected imidazolylalkanol under Mitsunobu conditions. Thereafter, the product is optionally reacted as described in Scheme 5.

Scheme 21

A compound 3 of Scheme 1 may be selectively reduced, e.g. by reaction with a reducing agent, such as borane in an inert organic solvent, such as, tetrahydrofuran at about room temperature. Thereafter, the product (2) is reductively aminated as described in Scheme 1.

Scheme 22Step 1

A compound 4 of Scheme 20 may be first reductively aminated as described in Step 5 of Scheme 1.

5

Step 2

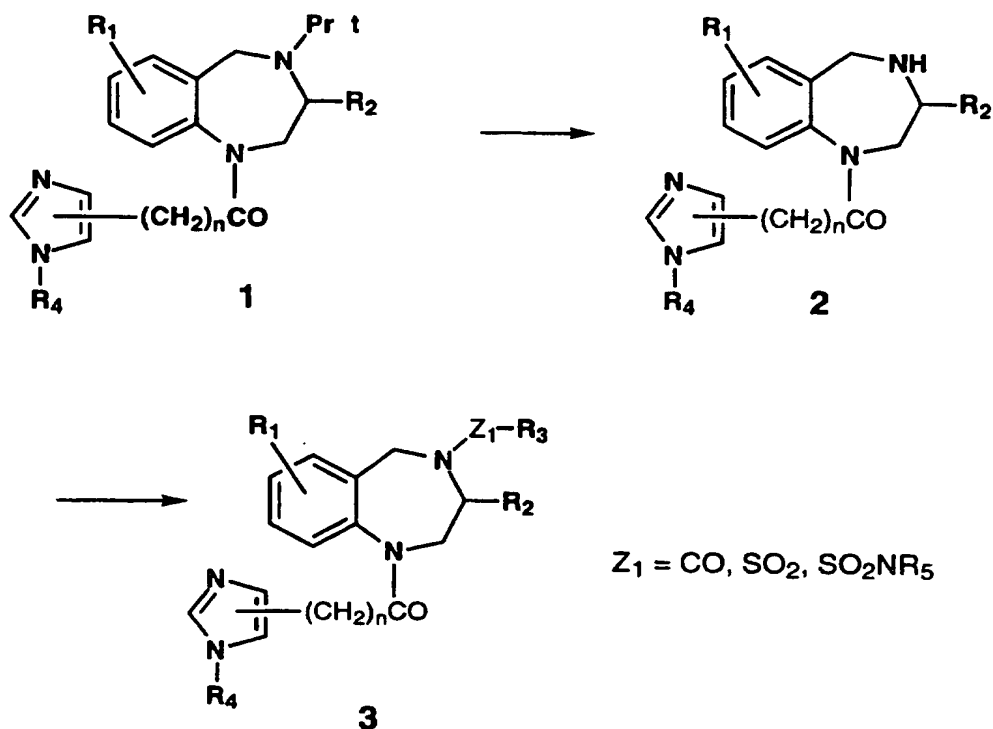
The optionally esterified ester of the product is hydrolyzed, e.g. by reaction with an alkali hydroxide in a suitable solvent such as aqueous alcohol at from room temperature to reflux.

10

Step 3

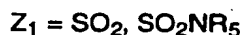
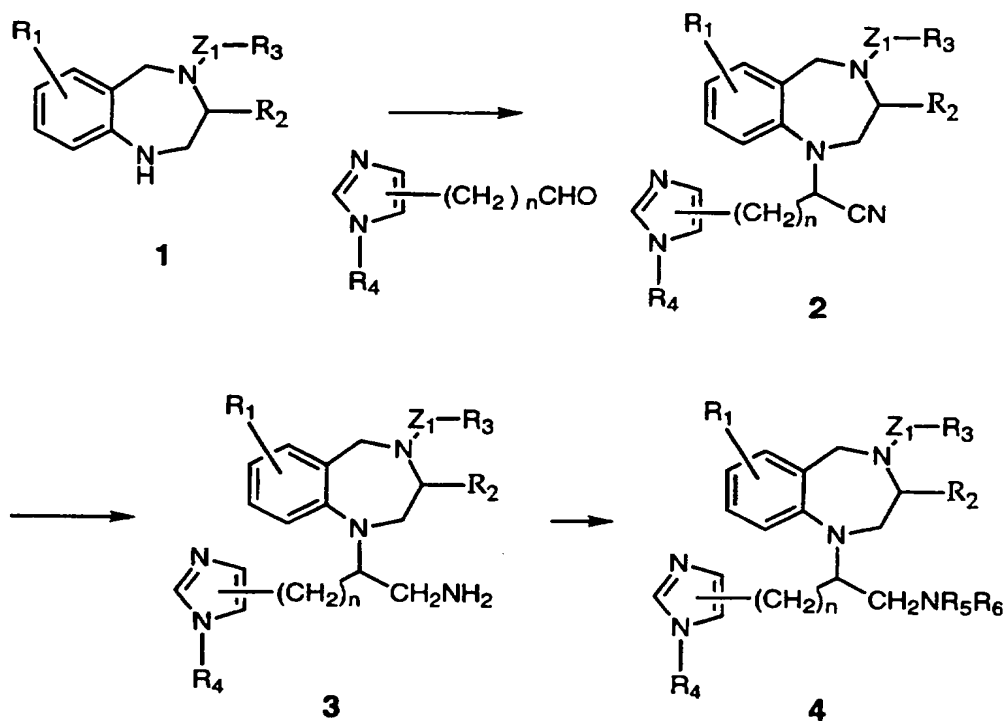
The product is cyclized by standard amide bond forming conditions, e.g. by reaction with BOP in an inert solvent such as DMF in the presence of an optional base such as diisopylethylamine at about room temperature.

15

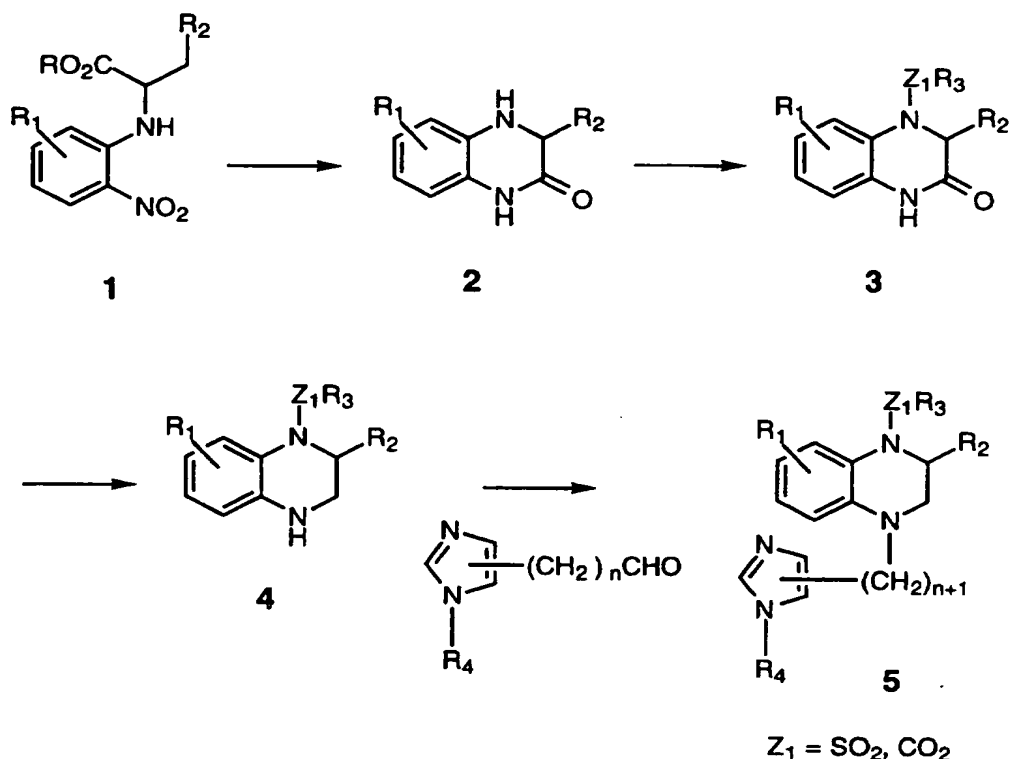
Scheme 23

A compound 2 of Scheme 12 may be directly deprotected as described in Step 3 of Scheme 12 and reacted as described in Step 4 of Scheme 12. Alternatively, a compound 5 of Scheme 12 may be prepared by reduction, e.g. with lithium aluminum hydride or borane, of a compound 3 of Scheme 23, where Z_1 does not equal CO.

Scheme 24

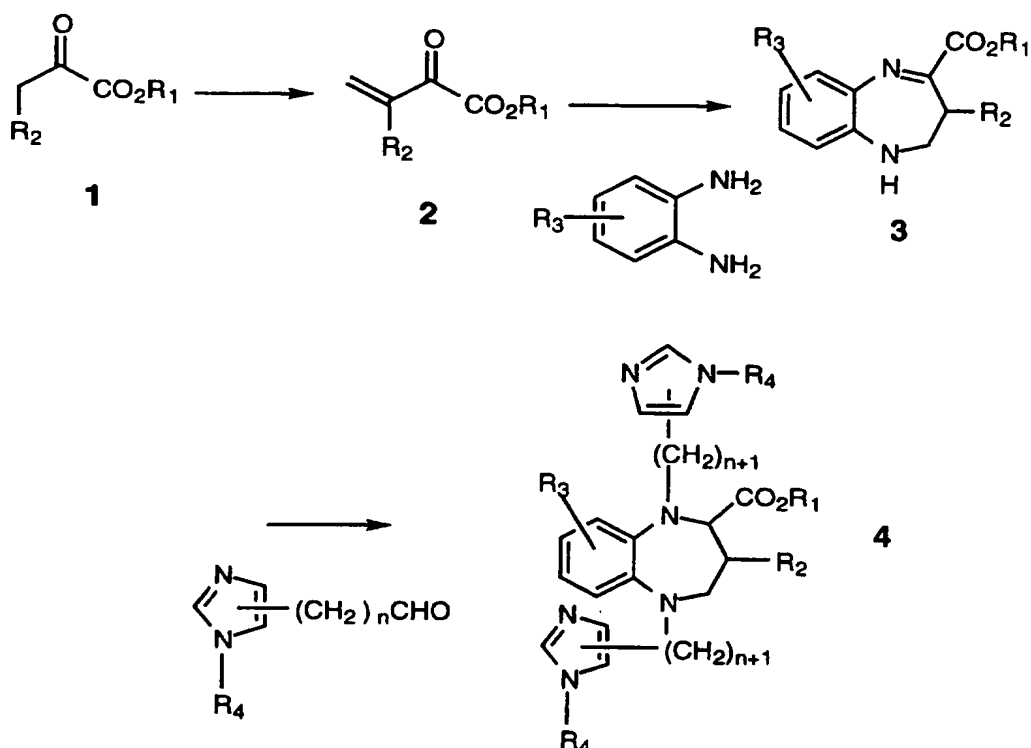


- A compound 5 of Scheme 1 may be reacted with an imidazole containing aldehyde and an alkali cyanide such as NaCN in the presence of an acid such as acetic acid in a suitable solvent such as methanol/acetonitrile at about room temperature to form a compound 2. The compound 2 may be reduced, e.g. with lithium aluminum hydride, in a suitable solvent such as ether at about room temperature to form a compound 3. The compound 3 wherein R₁ is halogen, e.g. bromine, may be prepared from the compound 3 wherein R₁ = H by reaction with a halogenating agent, e.g. tetrabutylammonium perbromide, in an inert solvent such as chloroform at about room temperature. The compound 3 may be reductively aminated under standard conditions to form the compound 4.

Scheme 25

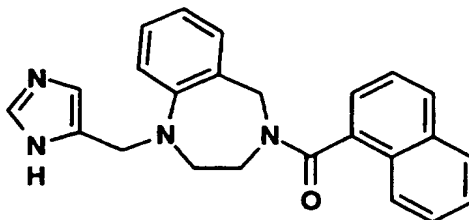
- In step 1 of Scheme 25, an N-(2-nitroaryl)-amino acid ester, available by reaction of an amino acid with a 1-fluoro-2-nitrobenzene followed by esterification, is reduced, e.g. with hydrogen and a palladium catalyst in a suitable solvent such as ethyl acetate at about room temperature. The resulting amine is cyclized to a compound 2 under the reduction conditions. The compound 2 is acylated or sulfonylated as described in Step 4 of Scheme 1. The compound 3 is reduced, e.g. with borane in a suitable solvent such as methanol at about room temperature. The compound 3 wherein R₁ is halogen, e.g. bromine, may be prepared from the compound 3 wherein R₁ = H by reaction with a halogenating agent, e.g. tetrabutylammonium perbromide, in an inert solvent such as chloroform at about room temperature. The compound 4 undergoes reductive amination with an imidazole containing aldehyde as described in Step 5 of Scheme 1.

Scheme 26



In step 1 of Scheme 26, the compound 1 is reacted with a methylenating agent such as N,N,N',N'-tetramethyl-diaminomethane in a suitable solvent such as acetic anhydride and DMF at about room temperature. Thereafter, the compound 2 is reacted with a 1,2-phenylenediamine in a suitable solvent such as toluene at about 115°C under dehydrating conditions, e.g. with a Dean-Stark trap, in the presence of a hydroquinone. Thereafter, the compound 3 is both reduced and reductively aminated as described in Step 5 of Scheme 1.

The invention will now be further described by the following working examples(s), which are preferred embodiments of the invention. All temperatures are in degrees Celsius ($^{\circ}\text{C}$) unless otherwise indicated. These examples are illustrative rather than limiting.

Example 1

5

2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, hydrochloride.

A. 1,4-Benzodiazepine-2,5-dione.

10 A stirred solution of isatoic anhydride (16.4 g, 0.1 mol) and glycine ethyl ester hydrochloride in 40 mL of pyridine was heated under reflux for 7 h. The resulting suspension was cooled to 0°C for 18 h. The precipitate was collected and washed with ethanol and ether to give Compound A as a light yellow solid.

15

B. 2,3,4,5-Tetrahydro-1H-1,4-benzodiazepine

To a stirred suspension of lithium aluminum hydride (LAH, 3.5 g, 90 mmol) in THF (100 mL) at room temperature under argon was slowly added Compound A (3.5 g, 20 mmol) portionwise as a solid. After the addition, the resultant suspension was heated at reflux under argon for 18 h, cooled to 0°C, and a mixture of NH₄OH (5 mL, conc.) in 30 mL of THF was added via an additional funnel. The resultant suspension was stirred for 1 h and filtered. The filtrate was concentrated in vacuo to give Compound B as an oil.

25

C. 2,3,4,5-Tetrahydro-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine

30 A mixture of Compound B (500 mg, 3.37 mmol) and 1-naphthoic acid, phenyl ester (750 mg, 3.02 mmol) in a small amount of acetonitrile in the presence of a catalytic amount of dimethylaminopyridine (DMAP) was heated at 110°C for 18 h under argon. The mixture was cooled to room temperature. The

product was isolated by flash column chromatography (1:1 ethyl acetate:hexanes) to give Compound C as a white solid (520 mg).

D. 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, hydrochloride

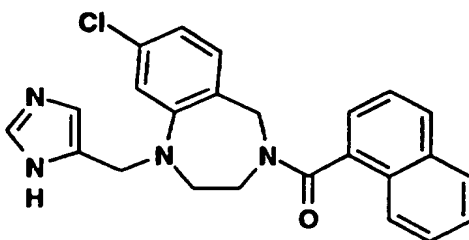
5 To a stirred solution of Compound C (200 mg, 0.66 mmol) and 4-formylimidazole (110 mg, 1.15 mmol) in a mixture of dichloroethane (2 mL) and acetic acid (1.0 mL), $\text{NaBH}(\text{OAc})_3$ (190 mg) was added in one portion. The mixture was stirred for 30 min and diluted with ethyl acetate (25 mL)
10 followed by NH_4OH (3 mL, conc.). The mixture was stirred at room temperature for 18 h and poured into a mixture of ethyl acetate (50 mL) and sat. NaHCO_3 (50 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (50 mL). The combined organic
15 extracts were washed with sat. NH_4Cl solution (50 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was dissolved in methanol (2 mL), and 1 N HCl solution in ether (2 mL) was added. The solvent was removed in vacuo and the residue was dried under vacuum to give Example 1 as a light yellow solid (240 mg).

MS: $(\text{M}+\text{H})^+$ 383+

20 Analysis calculated for $\text{C}_{24}\text{H}_{22}\text{N}_4\text{O} \cdot 1.75 \text{ HCl} \cdot 2.5 \text{ H}_2\text{O}$.

Calc'd: C, 58.67; H, 5.90; N, 11.41; Cl, 12.63.

Found: C, 58.48; H, 6.10; N, 11.32; Cl, 12.46.

Exempl 2

5 **8-Chloro-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, hydrochloride**

A. 8-Chloro-1,4-benzodiazepin-2,5-dione

A solution of 7-chloro-isatoic anhydride (34 g, 0.17 mol) and glycine ethyl ester hydrochloride (24 g, 0.17 mol) in anhydrous pyridine (120 ml) was
10 warmed at 80°C for 1 hour and refluxed overnight. The resulting suspension was stirred at room temperature for 3 hrs. The precipitate was filtered, washed with water and dried to give 4.4 g of Compound A as a white solid. The filtrate was evaporated and the resulting solid was washed with water
15 and dried to provide an additional 27.2 g of Compound A as a white solid (85% total yield). MS (M+H) 211.

B. 8-Chloro-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine

To Compound A (1.4 g, 6.6 mmol) in ethylene glycol dimethyl ether (20 ml) was added borane-THF (1.0 M in THF, 20 ml). The clear solution was
20 refluxed for 6 hrs. The solvent was evaporated and the residue was treated with sat. sodium bicarbonate. The aqueous solution was extracted with methylene chloride. The organic solution was washed with sat. sodium bicarbonate and brine, dried (sodium sulfate) and evaporated to afford an oil
25 (1.0 g). The crude product was purified by chromatography (10% methanol in methylene chloride) to provide Compound B as a slightly yellow solid (0.56 g, 46%). MS (M+H) 183.

C. 8-Chloro-2,3,4,5-tetrahydro-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine

To a solution of Compound B (0.154 g, 0.84 mmol) in methylene chloride (4 ml) and sodium hydroxide (1N, 4 ml) at 0°C was added 1-naphthoyl chloride (0.12 ml, 0.84 mmol) in methylene chloride (1 ml) dropwise. The solution

was stirred for 1 hour, the organic layer was separated and the aqueous layer was extracted with methylene chloride. The combined organic layers were dried (sodium sulfate) and evaporated. The resulting oil was chromatographed (silica, 5 % methanol, 0.5% ammonium hydroxide, 94.5% methylene chloride) to provide Compound C as a yellow solid (0.26 g, 90%). MS (M-H) 335.

D. 8-Chloro-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, hydrochloride

Compound D was prepared from Compound C as described for Compound D of Example 1. Chromatography (silica, 5% methanol, 0.5% ammonium hydroxide, 94.5% methylene chloride) followed by preparative HPLC and conversion to the hydrochloride salt provided Example 2 as an off white solid, m.p. 160-162°C.

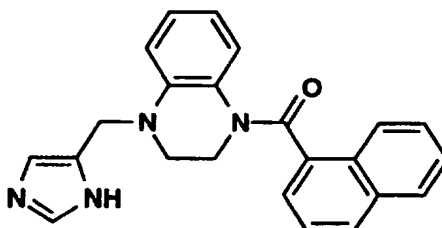
MS: (M+H)⁺ 383⁺

Analysis calculated for C₂₄H₂₁N₄OCl • 1.85 HCl • 2.5 H₂O.

Calc'd: C, 59.51; H, 4.76; N, 11.57.

Found: C, 59.42; H, 4.84; N, 11.48.

Example 3



1,2,3,4-Tetrahydro-4-[(3H-imidazol-4-yl)methyl]-1-(naphthalen-1-ylcarbonyl)quinoxaline, dihydrochloride.

A. 1,2,3,4-Tetrahydro-quinoxaline

Pt(IV)O₂ (Adams' catalyst, 200 mg) was added to a solution of quinoxaline (2.75 mg, 21 mmol) in absolute EtOH (100 mL) and the mixture was hydrogenated (1 atm) at rt for 6 hrs. The mixture was filtered through Celite and the filtrate was concentrated to give 2.74 g of Compound A as an off-white solid (97%). MS (M+H) 135.

B. 1,2,3,4-Tetrahydro-1-(naphthalen-1-ylcarbonyl)quinoxaline

Naphthoyl chloride (1.12 mL, 7.45 mmol) was added to a solution of Compound A (1.0g, 7.45 mmol) and triethylamine (TEA, 2.1 mL, 14.9 mmol) in CH₂Cl₂ (100 mL) at -78 °C. After 2 hrs, the cooling bath was removed the mixture was stirred at rt for 1 hr and concentrated. The residue was purified by flash chromatography (silica, 95:5:0.1, CHCl₃:MeOH:NH₄OH) to afford Compound B as an off-white solid (2.04 g, 95%). MS (M+H) 289.

C. 1,2,3,4-Tetrahydro-4-[(3H-imidazol-4-yl)methyl]-1-(naphthalen-1-ylcarbonyl)quinoxaline, dihydrochloride

Compound C was prepared from Compound B as described for Compound D of Example 1. Chromatography (silica, 10% ethanol/ethyl acetate) provided a clear yellow oil which was converted to the hydrochloride with 4N HCl in dioxane (4mL, rt for 2 hrs) to give Example 3 as an off-white solid.

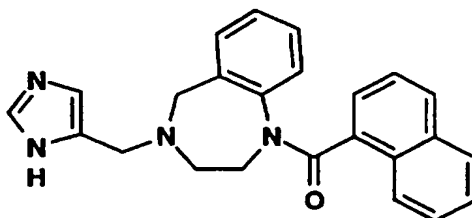
MS: (M+H)⁺ 289⁺

Analysis calculated for C₂₃H₂₀N₄O • 1.9 HCl.

Calc'd: C, 63.10; H, 5.04; N, 12.47.

Found: C, 63.10; H, 5.39; N, 12.47.

Example 4



2,3,4,5-Tetrahydro-4-(1H-imidazol-4-yl-methyl)-1-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, dihydrochloride,

A. 2,3,4,5-Tetrahydro-4-[(1,1-dimethylethoxy)-carbonyl]-1H-1,4-benzodiazepine

To a stirred solution of Compound B of Example 1 (300 mg) was added di-*t*-butyldicarbonate (400 mg). The mixture was stirred at room temperature for

18 h and quenched by the addition of sat. NaHCO_3 solution. The solvent was removed and the residue was chromatographed (flash, silica, 1:2 ethyl acetate:hexanes] to give Compound A as an oil (350 mg).

5 **B. 2,3,4,5-Tetrahydro-1-(1-naphthalenylcarbonyl)-4-[(1,1-dimethylethoxy)-carbonyl]-1H-1,4-benzodiazepine**

To a stirred solution of Compound A (350 mg, 1.4 mmol) in methylene chloride at 0°C under argon, was added 1-naphthoyl chloride (0.22 mL, 1.4 mmol), followed by pyridine (0.25 mL). The mixture was stirred for 2 h. Sat. NaHCO_3 was added and the mixture was stirred for 18 h at room temperature. The resultant solution was poured into a mixture of methylene chloride and sat. NaHCO_3 . The organic layer was separated, washed with 10% HCl (2 x 25 mL), dried (MgSO_4) and concentrated in vacuo to give to give Compound B as an oil (450 mg, 80%).

15 **C. 2,3,4,5-Tetrahydro-1-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine**

Compound B was dissolved in a mixture of methylene chloride and TFA (10 mL, 1:1). The solution was stirred at room temperature for 2 h. The solvent was removed in vacuo, the residue was diluted in CHCl_3 and made basic with 10 N NaOH solution. The organic layer was separated, dried (MgSO_4) and concentrated to give Compound C as an oil (310 mg, 92%).

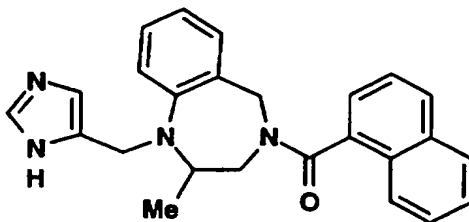
25 **D 2,3,4,5-Tetrahydro-4-(1H-imidazol-4-yl-methyl)-1-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, dihydrochloride**

Example 4 was prepared as a light yellow solid from Compound C as described for Compound D of Example 1.

Analysis calculated for $\text{C}_{24}\text{H}_{22}\text{N}_4\text{O} \cdot 2.0 \text{ HCl} \cdot 1.3 \text{ H}_2\text{O}$.

Calc'd: C, 60.20; H, 5.60; N, 11.70; Cl, 14.82.

30 Found: C, 60.21; H, 5.60; N, 11.48; Cl, 14.68.

Exempl 5

5 **2,3,4,5-Tetrahydro-1-(1H-imidazol-4-yl-methyl)-2-methyl-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, hydrochloride.**

A. 2-Methyl-1,4-benzodiazepin-3-one

10 The Boc derivative of Compound A was prepared from 2-amino-N-[(1,1-dimethylethoxy)-carbonyl]-phenylmethylamine and methyl pyruvate as described for Compound D of Example 1. The resulting oil was dissolved in a mixture of methylene chloride and TFA (8 mL, 1:1), the solution was stirred at room temperature for 1 h and concentrated in vacuo. The residue was partitioned between ether and 10% HCl solution and the aqueous solution
15 was made basic with 10N NaOH solution to pH 11 and extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were dried over MgSO₄ and concentrated to give Compound A as a solid (250 mg, 28%), mp: 149-151 °C. MS (M+H) 177.

20 **B. 2-Methyl-1,4-benzodiazepine**

A solution of Compound A (181 mg, 1.03 mmol) was added to a suspension of LAH (160 mg, 4.21 mmol) in anhydrous THF(5 mL) at room temperature dropwise. The solution was heated at reflux for 5 h, cooled to 0°C and diluted with THF (20 mL). Brine (0.5 mL) was added dropwise and the
25 mixture was stirred at room temperature for 18h and filtered through a pad of MgSO₄. The pad was washed with ethyl acetate and the combined filtrates were concentrated in vacuo to give Compound B as a semisolid (160 mg, 96%). MS (M+H) 163.

C. 2-Methyl-4-(1-Naphthalenylcarbonyl)-1,4-benzodiazepine

Compound C was prepared from Compound B as described for Compound C of Example 2. Chromatography (flash, silica, 1:1 ethyl acetate:hexanes) gave Compound C a solid, mp: 75°C. MS (M+H) 317.

D. 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-yl-methyl)-2-methyl-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, hydrochloride

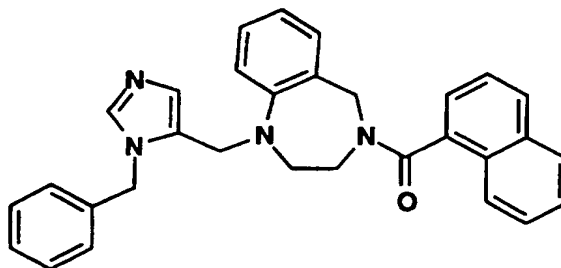
Example 5 was prepared as a light yellow solid from Compound C as described for Compound D of Example 1, mp: 165°C (foams). MS (M+H) 397.

Analysis calculated for $C_{25}H_{24}N_4O \cdot 2.4 HCl \cdot 1.0 H_2O \cdot 0.5 CH_3OH$.

Calc'd: C, 59.12; H, 5.92; N, 10.84; Cl, 16.42.

Found: C, 59.09; H, 5.58; N, 10.48; Cl, 16.28.

Example 6



2,3,4,5-Tetrahydro-4-(1-naphthalenylcarbonyl)-1-[[1-(phenylmethyl)-1H-imidazol-5-yl]methyl]-1H-1,4-benzodiazepine, hydrochloride.

A. 2,3,4,5-Tetrahydro-4-(1-naphthalenylcarbonyl)-1-[[1-(triphenylmethyl)-1H-imidazol-4-yl]methyl]-1H-1,4-benzodiazepine

To a solution of Example 1 (90 mg, 0.21 mmol) in acetonitrile (1 ml) at rt under argon was added TEA (0.14 μ L, 1 mmol) followed by triphenylmethylchloride (56 mg, 0.2 mmol). The mixture was refluxed for 2 hr, cooled to rt and stirred for 14 hr. The precipitate was filtered and the

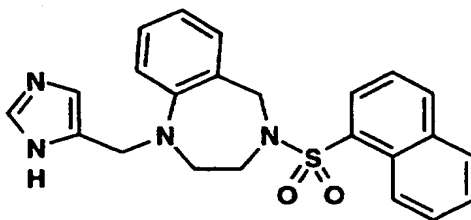
filtrate was concentrated to afford Compound A (110 mg, 92 %). MS (M+H)⁺ = 625.

B. 2,3,4,5-Tetrahydro-4-(1-naphthalenylcarbonyl)-1-[[1-(phenylmethyl)-1H-imidazol-5-yl]methyl]-1H-1,4-benzodiazepine, hydrochloride

To a solution of benzyl alcohol (18 μ L, 0.18 mmol) in THF (1 ml) at -78°C under argon was added triflic anhydride (30 μ L, 0.18 mmol) and DIPEA (35 μ L, 2 mmol). After 20 min, a THF (1 ml) solution of Compound A (100 mg, 0.15 mmol) was added dropwise. The mixture was allowed to warm to rt over 3 hr and was stirred for 14 hr. Acetic acid (1.5 ml) and water (1 ml) were added and the mixture was refluxed for 30 min, cooled to rt and evaporated. The residue was dissolved in chloroform and the solution was washed with saturated NaHCO₃ solution, dried (MgSO₄) and concentrated. The residue was chromatographed (flash, silica, 9:1 CHCl₃:MeOH). Clean product was dissolved in ethyl acetate and the solution was bubbled with HCl gas for 30 seconds. Evaporation afforded Example 6 (33 mg, 33% overall). MS (M+H)⁺ = 473. IR (KBr) 2853, 1630, 1508 cm⁻¹.

20

Example 7



2,3,4,5-Tetrahydro-1-(1H-imidazol-4-yl-methyl)-4-(1-naphthalenylsulfonyl)-1H-1,4-benzodiazepine, hydrochloride,

A. 2,3,4,5-Tetrahydro-4-(1-naphthalenylsulfonyl)-1H-1,4-benzodiazepine

Compound A was prepared from Compound B of Example 1 and 1-naphthalenesulfonyl chloride as described for Compound C of Example 2. Crystallization from methanol gave Compound A as a solid, mp 165-166 °C. MS (M+H)⁺ 339.

B. 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylsulfonyl)-1H-1,4-benzodiazepine, hydrochloride

Example 7 was prepared as a white solid from Compound A as described for Compound D of Example 1, mp 140 °C (foams).

5 MS (M+H) 419.

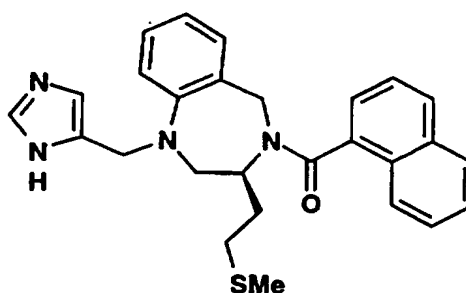
Analysis calculated for $C_{23}H_{22}N_4O_2S \cdot 1.5 HCl \cdot 1.0 H_2O$.

Calc'd: C, 56.34; H, 5.22; N, 11.43; Cl, 10.85; S, 6.54.

Found: C, 56.70; H, 5.16; N, 11.04; Cl, 10.72; S, 6.54.

10

Example 8



15 **(S)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-[2-(methylthio)ethyl]-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, hydrochloride.**

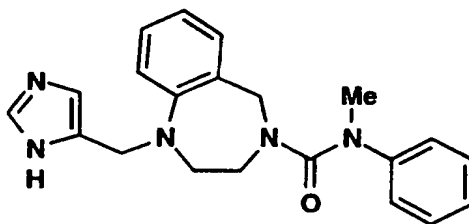
20 Example 8 was prepared as a yellow solid from isatoic anhydride and L-methionine methyl ester hydrochloride as described in the following multistep sequence: Compound A of Example 1; Compound B of Example 1, except that ethylene glycol dimethyl ether was used as solvent; Compound C of Example 2; Compound D of Example 1. mp 78-80°C.

MS (M+H) 457

25 Analysis calculated for $C_{27}H_{28}N_4OS \cdot 1.6 HCl \cdot 2.3 H_2O$.

Calc'd: C, 58.28; H, 6.20; N, 10.07; S, 5.76; Cl, 10.19.

Found: C, 58.02; H, 5.87; N, 12.23; S, 4.95; Cl, 10.27.

Exempl 9

5 **2,3,4,5-Tetrahydro-1-(1H-imidazol-4-yl-methyl)-N-methyl-N-phenyl-4H-1,4-benzodiazepine-4-carboxamide, hydrochloride,**

A. 2,3,4,5-Tetrahydro-N-methyl-N-phenyl-4H-1,4-benzodiazepine-4-carboxamide

10 To a stirred solution of the Compound B of Example 1 (0.5 g, 3.35 mmol) in THF in the presence of NaHCO₃ (1.68, 20 mmol) was added N-methyl-N-phenyl carbamoyl chloride (480 mg, 2.83 mmol). The mixture was stirred at room temperature for 18 h and filtered. The filtrate was concentrated in vacuo and the residue was crystallized from methanol to give Compound A
15 as a white solid (720 mg, 76%), mp: 159-160 °C.

B. 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-yl-methyl)-N-methyl-N-phenyl-4H-1,4-benzodiazepine-4-carboxamide, hydrochloride

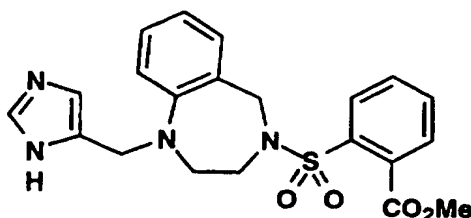
20 Example 9 was prepared as a white solid from Compound A as described for Compound D of Example 1, mp: 145°C (shrinks).

MS (M+H) 362

Analysis calculated for C₂₁H₂₃N₅O • 1.8 HCl • 1.0 H₂O.

Calc'd: C, 56.67; H, 6.07; N, 15.74; Cl, 14.34.

25 Found: C, 57.08; H, 6.03; N, 15.40; Cl, 14.53.

Example 10

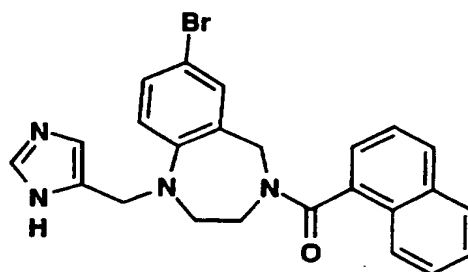
- 5 **2-[2,3,4,5-Tetrahydro-1-(1H-imidazol-4-yl-methyl)-1H-1,4-benzodiazepin-4-yl]sulfonyl]benzoic acid, methyl ester, hydrochloride,**

Example 10 was prepared as a white solid from 2-methoxycarbonylbenzenesulfonyl chloride and Compound B of Example 2
 10 as described in the following multistep sequence: Compound C of Example 2; Compound D of Example 1.

MS (M+H) 427

Analysis calculated for $C_{21}H_{22}N_4O_4S \cdot 1.1 \text{ HCl} \cdot 1.0 \text{ H}_2\text{O}$.

- 15 Calc'd: C, 52.04; H, 5.22; N, 11.56; S, 6.62; Cl, 8.05.
 Found: C, 52.20; H, 5.11; N, 10.40; S, 7.20; Cl, 8.09.

Example 11

- 20
 25 **7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, hydrochloride.**

A. 7-Br mo-1,4-b nzodiazepin-2,5-di n

Compound A was prepared from 6-bromoisatoic anhydride as described for Compound A of Example 1.

5 **B. 7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, hydrochloride.**

Example 8 was prepared as a solid from Compound A as described in the following multistep sequence: Compound B of Example 2; Compound C of Example 2; Compound D of Example 1. Chromatography (5% methanol, 0.5% ammonium hydroxide, 94.5% methylene chloride) followed by preparative HPLC and conversion into the hydrochloride salt provided Example 11, mp 160-162°C.

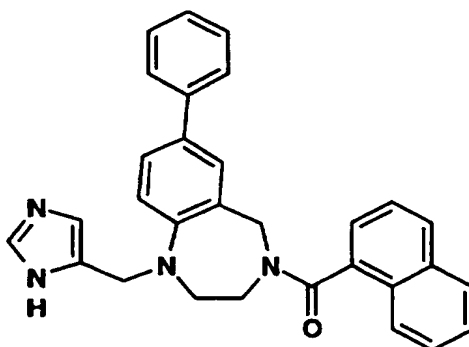
MS (M+H) 461

15 Analysis calculated for $C_{24}H_{21}BrN_4O \cdot 1.5 HCl$.

Calc'd: C, 55.86; H, 4.39; N, 10.86.

Found: C, 55.84; H, 4.49; N, 10.71.

20

Example 12

25 **2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-7-phenyl-1H-1,4-benzodiazepine, hydrochloride.**

A. 7-Phenyl-1,4-benzodiazepine-2,5-dione

A solution of Compound A of Example 11 (0.834 g, 3.1 mmol) in 20 mL of 1:1 DMF:THF was degassed with nitrogen. Tetrakis(triphenylphosphine) palladium was added. After half an hour, anhydrous sodium carbonate (0.37 g, 3.5 mmol) in water (6 ml) and phenylboronic acid (1.00 g, 8.3 mmol) were added. The suspension was stirred at room temperature overnight, then at 80-90°C for 2 days. The suspension was filtered. The precipitate was washed with water and ethyl acetate to give a Compound A as slightly grey solid (0.65 g, 84%). LC-MS (M+H)⁺ 253.

10

B. 7-Phenyl-1,4-benzodiazepine

To a suspension of Compound A (0.62 g, 2.5 mmol) in THF was added LAH in THF (1.0 M in THF, 7 ml). The suspension was stirred for 3 hrs and refluxed for 2 hrs. After cooling to rt, sodium hydroxide (1N, 5 ml) was added followed by 10 mL of saturated sodium potassium tartrate. The aqueous solution was extracted with methylene chloride. The organic phase was dried (sodium sulfate) and evaporated. The resulting oil was purified by chromatography (10% methanol in methylene chloride) to provide Compound B as a slightly yellow solid (0.46 g, 58%). LC-MS (M+H)⁺ 225.

20

C. 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-7-phenyl-1H-1,4-benzodiazepine, hydrochloride.

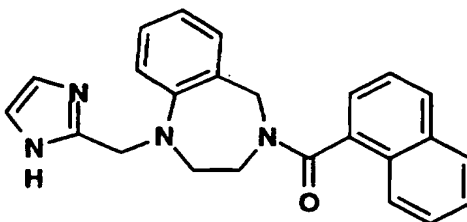
Example 12 was prepared as a solid from Compound B as described in the following multistep sequence: Compound C of Example 2; Compound D of Example 1. Chromatography (5% methanol, 0.5% ammonium hydroxide, 94.5% methylene chloride) followed by preparative HPLC and conversion into the hydrochloride salt provided Example 12, mp 158-160°C.

MS (M+H) 459

30 Analysis calculated for C₃₀H₂₆N₄O • 2.0 HCl • 0.58 H₂O.

Calc'd: C, 66.50; H, 5.42; N, 10.34.

Found: C, 66.56; H, 5.64; N, 10.00.

Example 13

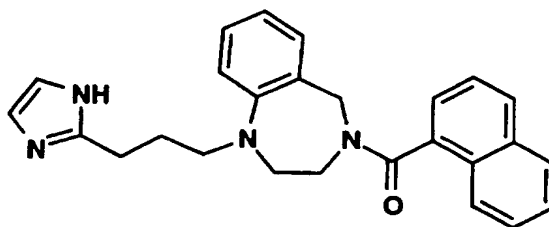
5 **2,3,4,5-Tetrahydro-1-(1H-imidazol-2-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, dihydrochloride.**

To a solution of Compound C of Example 1 (50 mg, 0.085 mmol) in dichloroethane (5 mL) was added 2-imidazole carboxaldehyde (33 mg, 0.34 mmol), NaBH(OAc)₃ (72 mg, 0.34 mmol) and glacial acetic acid (0.2 mL).
10

The mixture was stirred for 16 hr. Saturated aqueous sodium bicarbonate solution was added (0.5 mL) and the solution was concentrated to dryness. The residue was dissolved in a 50/50 mixture of 0.1%TFA in methanol and 0.1%TFA in water and applied to a YMC C18 column (S-5, ODS 30x250 mm). HPLC purification was performed under the following conditions;
15 Solvent A; 0.1%TFA in 90% water, 10% methanol, Solvent B; 0.1%TFA in 90% methanol, 10% water; 10-90%B in A over 30 minutes. Fractions containing the major peak were pooled and lyophilized to afford a white solid. 1 M HCl (6 mL) was added and the solution was concentrated to a glass.
20 This step was repeated to give 25 mg (66%) of Example 13 as a glassy white solid.

MS (M+H)⁺ 383

¹H-NMR (CD₃OD, 270 MHz) δ 8.11(2H, m), 7.7-7.1 (10H, m), 6.71 (0.5H, t, J=7.05 Hz), 6.07 (0.5H, d, J=7.05 Hz), 5.01(1H, m), 4.7-4.0 (2H, m), 3.6-
25 3.4(4H, m), 3.1(1H, m).

Example 14

5 **2,3,4,5-Tetrahydro-1-[3-(1H-imidazol-2-yl)propyl]-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, dihydrochloride.**

A. 3-[Imidazol-2-yl]-propenoic acid, ethyl ester

 To a cooled (0°C) solution of sodium hydride (1.86g, 45.8 mmol, 60%
10 dispersion in mineral oil, prewashed with THF and dried over N₂) in 1,2-dimethoxyethane (DME, 20 mL) was added triethylphosphonoacetate (12g, 54.1 mmol) dissolved in DME (10 mL) dropwise over 15 minutes. The solution was stirred for 1 hr at ambient temperature followed by the addition of 2-imidazole acetaldehyde (4 g, 41.6 mmol) in 20 mL of DME. The solution
15 was stirred and heated to reflux (85°C) for 15 minutes followed by cooling to 60°C for 1 hr. On cooling, the solution was concentrated to 1/2 volume and filtered. The solid was recrystallized from methanol/ethyl acetate/hexanes to give 5.1g (74%) of Compound A as a white crystalline solid. MS (M+H)⁺ 167⁺.

20 **B. 3-[Imidazol-2-yl]-propanoic acid, ethyl ester**

 A solution of Compound A (4.01g, 24.2 mmol) in absolute ethanol (100 mL, heated to dissolve) was hydrogenated using Pd/C (0.5g) at ambient temperature for 16 hr. Following removal of H₂ under vacuum, the catalyst
25 was removed by filtration through a bed of celite. The filtrate was concentrated under vacuum to give 4.0 g (100%) of Compound B as a white crystalline solid. MS (M+H)⁺ 169⁺.

30 **C. 3-[N-Triphenylmethyl-imidazol-2-yl]-propanoic acid, ethyl ester**

 Compound C was prepared from Compound B as described for Compound A of Example 6, using methylene chloride as solvent. After aqueous workup,

recrystallization from ethyl acetate/hexanes afforded Compound C as a white crystalline solid. MS (M+H)⁺ 411+.

D. 3-[N-Triphenylmethyl-imidazol-2-yl]-propanal

- 5 A stirred solution of Compound C (300 mg, 0.73 mmol) in dichloromethane (3 mL) was cooled to -78°C and a precooled (-70°C) solution of 1M DIBAL in dichloromethane (0.73 mmol, 0.73 mL) was introduced via syringe. After stirring for 1 h, an additional aliquot of precooled (-70°C) DIBAL solution (0.3 mL, 0.3 mmol) was added. After stirring for an additional 2 h, saturated
10 aqueous NH₄Cl was added (10 mL) followed by 0.1N HCl (20 mL). After stirring for 5 min, methylene chloride was added (30 mL). The layers were separated and the aqueous layer was washed with methylene chloride. The pooled organic layers were dried over MgSO₄, filtered and concentrated to yield 266 mg (99%) of Compound D as a white solid. ¹H-NMR(CD₃OD, 270
15 MHz) δ 9.4(1H, s), 7.38 (10H, m), 7.05 (7H, m), 2.7-2.2(4H, m).

E. 2,3,4,5-Tetrahydro-1-[3-(1-triphenylmethyl-imidazol-2-yl)propyl]-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine

- Compound E was prepared from Compound D and Compound C of
20 Example 1 as described for Compound D of Example 1, with stirring for 16 hours. Chromatography (flash, silica, 9:1 methylene chloride:methanol) afforded (74%) of Compound E as a glass. MS (M+H)⁺ 653.3.

F. 2,3,4,5-Tetrahydro-1-[3-(1H-imidazol-2-yl)propyl]-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, dihydrochloride

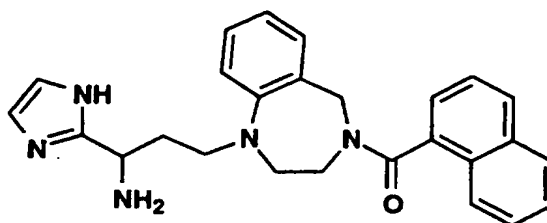
- 25 A mixture of Compound E (110 mg, 0.18 mmol) in TFA (5 mL), methylene chloride (5 mL) and triethylsilane (0.1 mL) was stirred for 2 h at room temperature and concentrated. Hexanes was added with stirring to the residue and the mixture was decanted. The residue was dissolved in a 50/50
30 mixture of 0.1%TFA in methanol and 0.1%TFA in water and was applied to a YMC C18 column (S-5, ODS 30x250 mm) and HPLC purification was performed under the following conditions; Solvent A; 0.1%TFA in 90% water, 10% methanol, Solvent B; 0.1%TFA in 90% methanol, 10% water; 0-100%B in A over 30 minutes. Fractions containing the major peak were pooled and
35 lyophilized to an oily residue. 1 M aqueous HCl (6 mL) was added and the solution was concentrated to a glass. This step was repeated to give 50 mg (84%) of Example 14 as a white solid.

MS (M+H)⁺ 411.

¹H-NMR (CD₃OD, 300 MHz) δ 8.05-7.95 (2H, m), 7.6-7.05 (12H, m), 6.71 (0.5H, m), 6.02(0.5H, m), 4.4 (2H, m), 3.6-3.0 (8H, m), 2.2-2.0(2H, m).

5

Example 15



10 **1-[3-Amino-3-(1H-imidazol-2-yl)propyl]-2,3,4,5-tetrahydro-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, trihydrochloride .**

A. N-[2-(trimethylsilyl)ethoxymethyl]imidazole

To a mixture of NaH (2.1g, 51 mmol, 60% dispersion in mineral oil, prewashed with hexanes) and DMF (60 mL) was added imidazole (3.0g, 44 mmol) in small portions. The mixture was stirred under N₂ for 1 h followed by the addition of 2-(trimethylsilyl)ethoxymethyl chloride (SEM-Cl) dropwis . The mixture was stirred for 1 h and quenched with water (5 mL). The mixture was poured into water (80 mL) and extracted with ethyl acetate. The organic layer was washed with saturated aqueous NH₄Cl, brine, dried (MgSO₄), filtered and concentrated to yield 6.3g (72%) of Compound A as a clear liquid. MS (M+H)⁺ 199.

B. N-[2-(trimethylsilyl)ethoxymethyl]imidazole-2-carboxaldehyde

25 To a cooled (-40°C) mixture of Compound A (3.0 g, 15.1 mmol) in THF (75 mL) was added a solution of nBuLi in hexane (2.5 M, 6.4 mL, 15.1 mmol). After 15 min, DMF (1.4 mL, 18.1 mmol) was added and the mixture was stirred for 3 h followed by addition of saturated aqueous NH₄Cl (30 mL). The mixture was extracted with ethyl acetate and the organic phase was washed with saturated aqueous NH₄Cl, brine, dried using MgSO₄, filtered and concentrated to yield 3.1g of Compound B (92%) as a light yellow oil. MS (2M+H)⁺ 453.2

C. 1-Amino-1-[N-[2-(trimethylsilyl)ethoxymethyl]imidazol-2-yl]-but-3-ene

To a cooled (-78°C) mixture of Compound B (1.22g, 5.4 mmol) in THF (10 mL) under Ar was added via syringe a precooled (-78°C) solution of lithium bistrimethylsilylamide in THF (1M, 5.6 mL, 5.6 mmol). The mixture was warmed to -20°C for 1 h and recooled to -78°C. To the mixture was added via syringe a precooled (-78°C) solution of allylmagnesium bromide (1M in ethyl ether, 7.45 mL, 7.45 mmol). The mixture was warmed to room temperature and stirred for 16 h under Ar. The mixture was quenched with 1N aqueous NaOH (20 mL) and extracted with ethyl ether. The organic layer was washed with brine, dried using MgSO₄, filtered and concentrated to a yellow residue. The residue was chromatographed on a flash silica gel column (5x20 cm) eluting with methylene chloride:methanol (9:1) followed by ammonium hydroxide:methanol:chloroform (1:5:94) to yield 0.55 g (38%) of Compound C an orange liquid. MS (M+H)⁺ 267.

D. 1-[(Triethylsilyl)ethoxycarbonylamino]-1-[N-[2-(trimethylsilyl)ethoxymethyl]imidazol-2-yl]-but-3-ene

To a stirred suspension of Compound C (450 mg, 1.7 mmol) in water (2 mL) was added a solution of TEA (0.32 mL, 2.3 mmol) in dioxane (2 mL) followed by 2-(triethylsilyl)ethoxycarbonylsuccinimide. The mixture was stirred at room temperature for 16 h. Ethyl ether (30 mL) and 1N aqueous KHSO₄ (30mL) were added. The layers were separated and the aqueous layer was washed with ethyl ether. The pooled organic layers were dried using MgSO₄, filtered and concentrated. The residue was chromatographed on a flash silica gel column (5x20 cm) eluting with methylene chloride:methanol (9:1) to yield 531 mg (84%) of Compound D as a glass. MS (M+H)⁺ 412.

E. 3-[(Triethylsilyl)ethoxycarbonylamino]-3-[N-[2-(trimethylsilyl)ethoxymethyl]imidazol-2-yl]-propanal

To a stirred mixture of Compound D in dioxane (5 mL) and water (5 mL) was added sodium periodate (94 mg, 0.37 mmol) and osmium tetroxide (2 mg dissolved in 0.5 mL water, 0.5 mL dioxane). The mixture was stirred for 18 h. Methylene chloride was added, the layers were separated and the aqueous layer was washed with methylene chloride. The combined organic layers were dried using MgSO₄, filtered and concentrated. The residue was chromatographed on a flash silica gel column (5x20 cm) eluting with

methylene chloride:methanol (9:1) to yield 90 mg (90 %) of Compound E as a glass.

F. 1-[[[(Tri thylsilyl)ethoxycarbonylamino]-3-(1-(trimethylsilyl)ethoxymethyl-imidazol-2-yl)propyl]-2,3,4,5-tetrahydro-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine

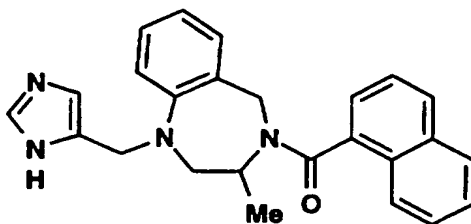
Compound F was prepared from Compound E and Compound C of Example 1 as described for Compound D of Example 1, with stirring for 16 hours. Chromatography (flash, silica, 9:1 methylene chloride:methanol) afforded (44%) of Compound F as a glass. MS (M+H)⁺ 700.

G. 1-[3-Amino-3-(1H-imidazol-2-yl)propyl]-2,3,4,5-tetrahydro-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, trihydrochloride

To a solution of Compound F (20 mg, 0.029 mmol) in THF (3 mL) was added tetrabutylammonium fluoride (44 mg, 0.17 mmol) and the solution was heated to 50°C for 16 h. On cooling, the solvent was removed under vacuum and the residue was dissolved in a 50/50 mixture of 0.1%TFA in methanol and 0.1%TFA in water and applied to a YMC C18 column (S-5, ODS 30x250 mm). HPLC purification was performed under the following conditions; Solvent A; 0.1%TFA in 90% water, 10% methanol, Solvent B; 0.1%TFA in 90% methanol, 10% water; 0-100%B in A over 30 minutes. Fractions containing the major peak were pooled and lyophilized to an oily residue. 1 M aqueous HCl (6 mL) was added and the solution was concentrated to a white solid. This step was repeated to give 9 mg (58%) of Example 15 as a white solid.

MS (M+H)⁺ 425

¹H-NMR (CD₃OD, 270 MHz) δ 8.05-7.95 (2H, m), 7.7-7.05 (10H, m), 6.71 (0.5H, m), 6.02(0.5H, m), 4.4 (2H, m), 4.0 (1H,m), 3.6-3.0 (7H, m), 2.9 (1H, m).

Example 16

- 5 **2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-methyl-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, hydrochloride.**

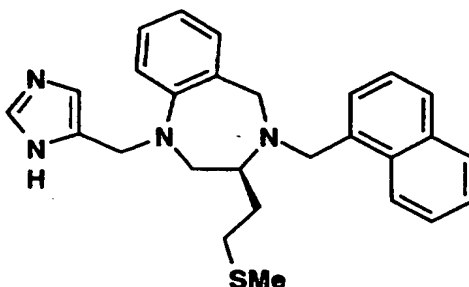
Example 16 was prepared as a yellow solid from isatoic anhydride and D,L-alanine ethyl ester hydrochloride as described for Example 8, mp 180-185°C.

MS (M+H)⁺ 397

Analysis calculated for C₂₅H₂₄N₄O • 1.3 HCl • 1.3 H₂O.

Calc'd: C, 64.26; H, 6.02; N, 11.99; Cl, 9.86.

Found: C, 64.33; H, 5.82; N, 11.70; Cl, 9.65.

Example 17

- 20 **(S)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-[2-(methylthio)ethyl]-4-(1-naphthalenylmethyl)-1H-1,4-benzodiazepine, hydrochloride.**

To a suspension of ethylene glycol dimethyl ether (anhydrous, 20 mL) and lithium aluminum hydride (17 mg, 0.45 mmol) under argon at 0° C was slowly added a mixture of Example 8 (75 mg, 0.15 mmol) in ethylene glycol dimethyl ether. The mixture was allowed to warm to room temperature, stirred for 30 min. and heated to reflux (85°C) for 18 hours. The mixture was

cooled to 0°C and quenched sequentially with a mixture of tetrahydrofuran and water (1 mL each), aqueous sodium hydroxide, (2 mL, 1N) and water (1 mL). The resultant precipitate was removed by filtration and the filtrate was concentrated in vacuo to yield an amber oil. This material was dissolved in methanol (2 mL), treated with a solution of hydrogen chloride (1 mL, anhydrous, 2M in ether), and concentrated in vacuo to yield Example 17 as a yellow solid, mp 115-120 °C.

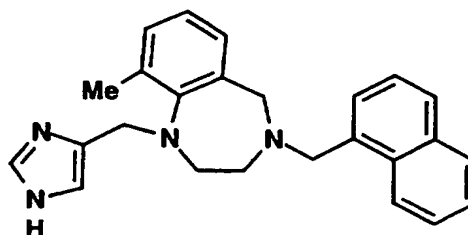
MS (M+H)⁺ 443

Analysis calculated for C₂₇H₃₀N₄S • 2.4 HCl • 2.6 H₂O.

10 Calc'd: C, 56.21; H, 6.57; N, 9.71; Cl, 14.75.

Found: C, 56.20; H, 6.55; N, 9.85; Cl, 14.81.

Example 18



15

2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-9-methyl-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, dihydrochloride.

20 Example 18 was prepared as a light yellow solid from 8-methyl isatoic anhydride and glycine ethyl ester hydrochloride as described in the following multistep sequence: Compound A of Example 1, with refluxing for 16 hours; Example 17, except that THF was used as solvent; refluxing with the 4-nitrophenyl ester of 1-naphthoic acid in toluene in the presence of DMAP; Compound D of Example 1.

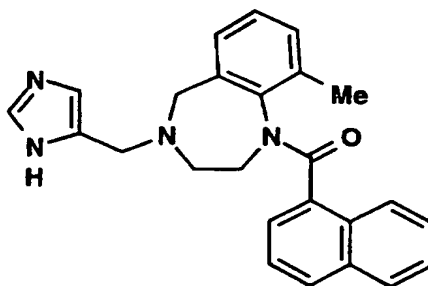
25 MS (M+H)⁺ 397

Analysis calculated for C₂₅H₂₄N₄O • 2 HCl.

Calc'd: C, 63.96; H, 5.58; N, 11.93.

Found: C, 62.83; H, 5.77; N, 11.13.

30

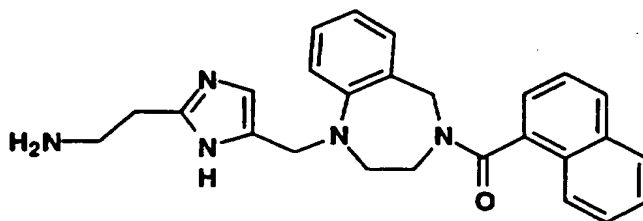
Exempl 19

- 5 **2,3,4,5-Tetrahydro-4-(1H-imidazol-4-ylmethyl)-9-methyl-1-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, dihydrochloride.**

Example 19 was prepared from 9-methyl-2,3,4,5-tetrahydro-1,4-benzodiazepine as described in the following multistep sequence:

- 10 Compound A of Example 4; coupling with 1-naphthoyl chloride using triethylamine in methylene chloride; Boc removal with 4N HCl in dioxane; Compound D of Example 1; chromatography (silica, flash, 9/1 CHCl₃/CH₃OH) followed by treatment with 1M HCl in ether and trituration with ether afford Example 19 as a light yellow solid..
- 15 **MS (M+H)⁺ 397**
¹H NMR (270 MHz, CD₃OD) δ 9.12 -8.9 (m, 1H), 8.5-8.23 (m, 1H), 8.1-7.9 (m, 3H), 7.9-7.0 (m, 7 H), 5.7-5.28 (m, 1H), 4.85-4.1 (m, 3H), 4.0-3.05 (m, 4 H), 2.9-2.55 m, 1H), 1.9-1.75 (s, 3H).

20

Example 20

- 25 **1-[[2-(2-Aminoethyl)-1H-imidazol-4-yl]methyl]-2,3,4,5-tetrahydro-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, trihydrochloride.**

A. [2-(2-[(1,1-dimethyl)-ethoxycarbonylamino]ethyl)-1-[(1,1-dimethyl)-ethoxycarbonyl]-imidazol-4-yl]methanol

[2-(2-Aminoethyl)-1H-imidazol-4-yl]methanol hydrochloride was prepared as described (Buschauer, et. al., Arch. Pharm., 315, 563, (1982)). To a suspension of 1.0 g of this crude material (assumed 4.7 mmol) in 10 mL of DMF was added 2 mL (14.1 mmol) of triethylamine and the slurry was stirred for 0.5 hr. To the reaction was then added 3.1 g (14.1 mmol) of BOC anhydride and stirring was continued overnight at rt. The reaction was evaporated to dryness and the residue subjected to flash chromatography on a 100 cc column of silica gel. Elution with ethyl acetate afforded 1.27 g (3.7 mmoles, 79 %) of Compound A as a viscous yellow oil.

B. [2-(2-[(1,1-dimethyl)-ethoxycarbonylamino]ethyl)-1-[(1,1-dimethyl)-ethoxycarbonyl]-imidazol-4-yl]carboxaldehyde

To a solution of 1.2 g (3.5 mmol) of Compound A in 10 mL of chloroform was added 0.9 g (10 mmol) of manganese dioxide. The reaction was heated at 50° C with vigorous stirring. Additional 0.3 g portions of MnO₂ were added after 1, 2 and 4 hrs of heating. After 6 hr at 50° C, the mixture was cooled to room temperature and without workup, was subjected to flash chromatography on a 150 cc column of silica gel. Elution with 50 % ethyl acetate-hexane afforded 673 mg (57 %) of Compound B as a white crystalline solid.

C. 1-[[2-(2-Aminoethyl)-1H-imidazol-4-yl]methyl]-2,3,4,5-tetrahydro-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, trihydrochloride

Compound C of Example 1 was reductively aminated with Compound B as described for Compound D of Example 1. The resulting oil was subjected to flash chromatography (silica, 50 % ethyl acetate-hexanes) to afford the bis-Boc analog of Compound C as a white foam. A solution of 94 mg (0.15 mmol) of this material in 3 ml of 4 N HCl-dioxane was stirred for 3 hr at rt. Removal of solvent gave a white foam residue which was subjected to preparative HPLC on a YMC S5 ODS (30 x 250 mm) column. Gradient elution from 0 to 100% solvent B (A: 10% methanol:water + 0.1% TFA, B: 10% water:methanol + 0.1% TFA) afforded an oil residue which was converted to its HCl salt by the addition of methanolic HCl and removal of

solvent. The residue was vaporated from methanol twice more to afford 53 mg (0.10 mmole, 66 %) of Example 20 as a white solid, mp 165°C.

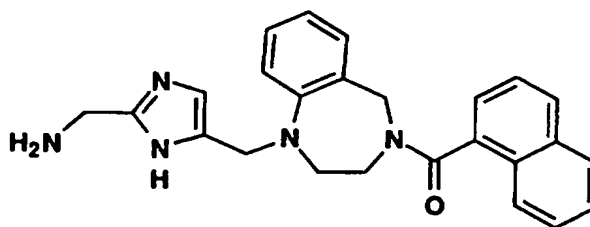
MS (M+H)⁺ 426

Analysis calculated for C₂₆H₂₇N₅O • 3 HCl.

5 Calc'd: C, 58.38; H, 5.65; N, 13.09.

Found: C, 59.01; H, 6.15; N, 13.03.

Example 21



10

1-[[2-(2-Aminomethyl)-1H-imidazol-4-yl]methyl]-2,3,4,5-tetrahydro-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, trihydrochloride.

15

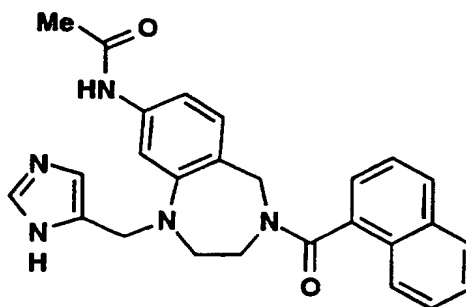
Example 21 was prepared as a white solid from chloroacetonitrile and Compound C of Example 1 as described for Example 20, mp 155-160°C.

MS (M+H)⁺ 412

Analysis calculated for C₂₅H₂₅N₅O • 3 HCl.

20 Calc'd: C, 57.65; H, 5.42; N, 13.45.

Found: C, 57.41; H, 5.18; N, 13.17.

Example 22

- 5 **N-[2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepin-8-yl]acetamide, dihydrochloride.**

10 **A. 2-[2-[[[(1,1-Dimethyl)-ethoxycarbonyl]amino]ethylamino]-4-nitro-benzoic acid**

Sodium cyanoborohydride (2.3 g, 38 mmol) was added portionwise to a solution of 2-[[[(1,1-dimethyl)-ethoxycarbonyl]amino]acetaldehyde (6.0 g, 38 mmol), 4-nitroanthranilic acid (3.8 g, 19 mmol) and acetic acid (2.0 ml) in methanol (150 ml). The mixture was stirred at room temperature for 16h, concentrated under vacuum, quenched with 1N HCl (100 ml) and extracted with CH₂Cl₂ (3x100 ml). The combined organic extracts were dried (MgSO₄), filtered and concentrated under vacuum. The residue was purified by flash chromatography (19 / 1 / 0.05 CHCl₃ / MeOH / AcOH) to afford Compound A (4.4 g, 72%) as a solid. MS: (M+H)⁺ 326

20

B. 2-[(2-amino)ethylamino]-4-nitro-benzoic acid

Anhydrous HCl in dioxane (4M, 20 ml, 80 mmol) was added to Compound B (2.8 g, 8.6 mmol) at room temperature and the mixture was stirred for 2h. The solution was concentrated under vacuum and the residue was triturated with diethyl ether to afford Compound B (2.1 g, 84%) as a solid. MS: (M+H)⁺ 226

25

C. 8-Nitro-2,3,-dihydro-1H-1,4-benzodiazepin-5-one

Diphenylphosphoryl azide (1.1 ml, 5.0 mmol) was added to a solution of Compound B (1.0 g, 3.4 mmol) in DMF (12 ml) at room temperature. The mixture was stirred for 10 minutes, N-methyl morpholine (1.3 ml, 12 mmol)

30

was added and the mixture was stirred at room temperature for 5h. The mixture was quenched with 10% LiCl /10% NaHCO₃ (100 ml) and the aqueous solution extracted with ethyl acetate (5X50 ml). The combined organic extracts were washed with 10% LiCl (2X60 ml), dried (MgSO₄),
5 filtered and concentrated under vacuum. The residue was triturated with petroleum ether and diethyl ether to afford Compound C (0.42 g, 61%) as a solid. MS: (M+CH₃CN+H)⁺ 249

D. 8-Nitro-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine

- 10 Borane dimethyl sulfide (10 M, 1.2 ml, 12 mmol) was added dropwise to solution of Compound C (0.42 g, 2.0 mmol) in THF (5 ml) at 0°C. The mixture was warmed to room temperature and then heated to reflux for 2h. The mixture was cooled to 0°C, methanol (10 ml) was carefully added and the solution was saturated with anhydrous HCl. The mixture was heated
15 to reflux for 1h, concentrated under vacuum and triturated with diethyl ether to afford Compound D (0.34 g, 65%) as a solid. MS: (M+H)⁺ 194

E. 8-Nitro-2,3,4,5-tetrahydro-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine

- 20 Compound E was prepared from Compound D and 1-naphthoyl chloride as described for Compound C of Example 2, with stirring for 16 hours. MS: (M+CH₃CN+H)⁺ 389

F. 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-8-nitro-1H-1,4-benzodiazepine

- 25 Compound F was prepared from Compound E as described for Compound D of Example 1, except that methanol was used as solvent and the free base was carried on to the next reaction. MS (M+H)⁺ 428

G. 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-8-amino-1H-1,4-benzodiazepine

- 30 Iron powder (0.15 g, 2.6 mmol) was added to a solution of Compound F (0.13 g, 0.29 mmol) in 500/50/1 ethanol / water / concentrated HCl (26 ml) at room temperature. The mixture was heated to reflux for 3h, cooled to room
35 temperature, filtered and the filtrate was concentrated under vacuum. The residue was dissolved in CH₂Cl₂ (100 ml), washed with 1N NaOH (100 ml), and the aqueous layer reextracted with CH₂Cl₂ (2X100 ml). The combined

organic extracts were dried (MgSO₄), filtered and concentrated under vacuum to afford Compound G (0.60 g, 52%) as a solid which was used without further purification.

H. N-[2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepin-8-yl]acetamide, dihydrochloride

4-Dimethylaminopyridine (0.005 g) was added to a solution of Compound G (0.050 g, 0.13 mmol) and acetic anhydride (0.024 ml, 0.25 mmol) in CH₂Cl₂ (2 ml) at room temperature. The mixture was stirred for 16h, quenched with 10% NaHCO₃ (1 ml) and MeOH (0.50 ml) and stirred at room temperature for 15 minutes. The mixture was diluted with water (5 ml) and the solution extracted with CH₂Cl₂ (3X50 ml). The combined organic extracts were dried (MgSO₄), filtered and concentrated under vacuum. The residue was purified by flash chromatography (19 / 1 / 0.01 CHCl₃ / MeOH / NH₄OH) and the appropriate fractions were concentrated under vacuum. The residue was dissolved in MeOH (5 ml), treated with 1N HCl (2 ml), millipore filtered and lyophilized to afford Example 22 (0.018 g, 32%) as a solid.

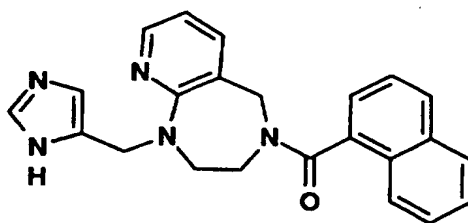
MS (M+H)⁺ 440

Analysis calculated for C₂₆H₂₅N₅O₂ • 2.0 HCl • 1.16 CH₃OH.

Calc'd: C, 59.35; H, 5.80; N, 12.74

Found: C, 59.35; H, 5.81; N, 12.22.

Example 23



2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-pyrido[2,3-e]-1,4-diazepine, trihydrochloride.

A. 2,3,4,5-Tetrahydro-1H-pyrido[2,3-e]-1,4-diazepin-5-one

A solution of 2-chloronicotinamide (4.0 g, 25.5 mmol) in ethylenediamine (25 mL) was heated to reflux for 24 hours. To the solution was added 5 N NaOH (5.1 mL, 25.5 mmol) and the mixture was concentrated in vacuo. The crude material was chromatographed (silica, 5-20% CH₃OH/CHCl₃) to give
5 Compound A (339 mg, 8%) as a light yellow solid. MS (M+H+CH₃CN)⁺ 205.

B. 2,3,4,5-Tetrahydro-1H-pyrido[2,3-e]-1,4-diazepine

To a solution of Compound A (100 mg, 0.61 mmol) in dry toluene (15 mL)
10 was added diisobutylaluminum hydride (1M in hexanes, 3.1 mL, 3.1 mmol). The mixture was warmed to reflux for 36 hours. At 12 and 24 hours, an additional portion of DiBAH was added (3.1 mL each time). At the end of 36 hours, the reaction was cooled to room temperature and quenched with
15 methanol. A viscous gel was formed which was dissolved in 1N HCl. The mixture was extracted with EtOAc (15 mL) and the organic layer discarded. The aqueous layer was made basic with 5N NaOH and extracted with 10% *i*-PrOH/CH₂Cl₂ (5x15 mL). The organic layers were combined, dried over Na₂SO₄, and concentrated in vacuo to afford Compound B (79 mg, 87%) which was carried on directly. MS (M+H+CH₃CN)⁺ 191.

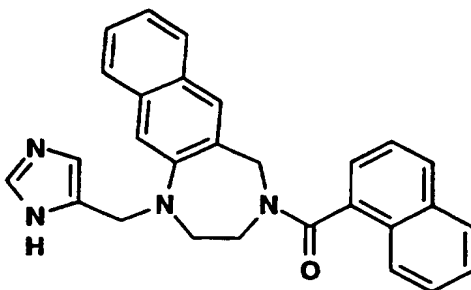
20

C. 2,3,4,5-Tetrahydro-4-(1-naphthalenylcarbonyl)-1H-pyrido[2,3-e]-1,4-diazepine

To a solution of Compound B (79 mg, 0.53 mmol), 1-naphthoic acid (115.5 mg, 0.67 mmol), EDC (128.4 mg, 0.67 mmol), and HOBt (90.5 mg, 0.67
25 mmol) in anhydrous DMF (2 mL) was added diisopropylethylamine (0.1 mL, 0.67 mmol). After 3 hours, the reaction was diluted with EtOAc (5 mL) and washed with 10% LiCl. The organic layer was washed with 1N HCl and discarded. The aqueous layer was made basic with 5N NaOH and extracted with EtOAc (5x5 mL). The five organic layers were combined and dried over
30 Na₂SO₄ and concentrated. The crude material was chromatographed (silica, 0-5% CH₃OH/CHCl₃) to give Compound C (96 mg, 60%) as a light brown oil. MS (M+H+CH₃CN)⁺ 345.

D. 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-pyrido[2,3-b]-1,4-diazepine, trihydrochloride

To a solution of Compound C (30 mg, 0.10 mmol) and 4-formyl imidazole (14.5 mg, 0.50 mmol) in dichloroethane (0.5 mL) and acetic acid (0.25 mL) was added NaBH(OAc)₃ (29.7 mg, 0.14 mmol). The mixture was stirred at room temperature for 12 hours and at 80°C for 12 hours. Additional portions of 4-formyl imidazole (14.5 mg, 0.50 mmol) and NaBH(OAc)₃ (30 mg, 0.14 mmol) were added and the reaction was warmed to 80°C for an additional 24 hours. The reaction was cooled to room temperature and diluted with EtOAc (2 mL) and NH₄OH (conc., 2 mL) was added. After stirring for 3 hours, NaHCO₃ (sat., 3 mL) was added along with more EtOAc (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3x5 mL). The organic layers were combined and washed with NH₄Cl (sat., 5 mL), dried over Na₂SO₄, and concentrated in vacuo. The crude material was diluted in methanol (2 mL) and purified by HPLC (YMC S5 ODS 30X250 mm column, solvent A: 10% MeOH/H₂O w/ 0.1% TFA, solvent B: 90% MeOH/H₂O w/ 0.1% TFA, gradient: 0-100%B in A over 60 min at a rate of 25 mL/min, monitored at 220 nm). The fractions containing the product were combined, concentrated in vacuo, dissolved in 1N HCl and lyophilized, dissolved in water and lyophilized again to give Example 23 as a fluffy white solid (4 mg, 8%). ¹H-NMR (CD₃OD, 400 MHz) δ 8.87 (d, J₁ = 1.3, 0.5H), 8.70 (d, J₁ = 1.3, 0.5H), 8.06 (dd, J₁ = 1.7, J₂ = 5.6, 0.5H), 7.96 (d, J₁ = 6.8, 0.5H), 7.83-7.91 (m, 2.5H) 7.60 (d, J₁ = 1.3, 0.5H), 7.52 (dd, J₁ = 1.7, J₂ = 7.3, 0.5H), 7.34-7.49 (m, 4H), 7.26 (dd, J₁ = 1.3, J₂ = 7.6, 0.5H), 7.11 (dd, J₁ = 1.3, J₂ = 7.1, 0.5H), 7.05 (dd, J₁ = 5.6, J₂ = 7.3, 0.5H), 6.57 (d, J₁ = 7.3, 0.5H), 6.52 (dd, J₁ = 5.6, J₂ = 7.7, 0.5H), 5.01 (d, J₁ = 1.3, 1H), 4.95 (d, J₁ = 1.3, 1H), 4.39-4.57 (m, 1.5H), 4.08-4.13 (m, 1H), 3.88-3.94 (m, 1H), 3.53-3.65 (m, 1.5H), 3.42-3.45 (m, 1H); MS (M+H)⁺ 384.

Example 24

- 5 **2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-naphtho[2,3-e]-1,4-diazepine, dihydrochloride.**

A. 2H-3,1-Naphthoxazine-2,4(1H)-dione

- 10 To an ice cooled slurry of 25 g (10.7 mmol) of 80% 2-amino-3-naphthoic acid and 2.5 g (8.5 mmol) of triphosgene in 70 mL of acetonitrile, under argon, was added dropwise 0.35 mL (25 mmol) of triethylamine. Stirring was continued while the cooling bath was allowed to warm to room temperature and then overnight at room temperature. To the resulting suspension was
- 15 then added 2 mL of methanol and stirring was continued for an additional hour. Filtration of the solid afforded 2.5 g (assumed 100 %) of crude Compound A as a light brown powder.

B. 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-naphtho[2,3-e]-1,4-diazepine, dihydrochloride

- 20 Example 24 was prepared as an amorphous off-white solid from Compound A by the following multistep sequence: Compound A of Example 1, with refluxing for 10 hours; Compound B of Example 2, except that THf was used as solvent and the product:borane complex was decomposed with refluxing
- 25 aqueous HCl; Compound C of Example 2, except that chromatography was done with 50% ethyl acetate-hexane afforded; Compound D of Example 1, with the product purified by prep HPLC (YMC S5 ODS (30x250 mm) column, gradient elution from 40 to 100% solvent B (A: 10% methanol:water + 0.1%
- 30 TFA, B: 10% water:methanol + 0.1% TFA) and converted to the HCl salt by treatment with HCl-MeOH.

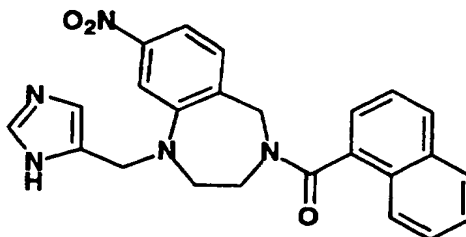
Analysis calculated for $C_{28}H_{24}N_4O \cdot 1.5 HCl \cdot 0.25 H_2O$.

Calc'd: C, 68.39; H, 5.33; N, 11.39.

Found: C, 68.41; H, 5.46; N, 11.31.

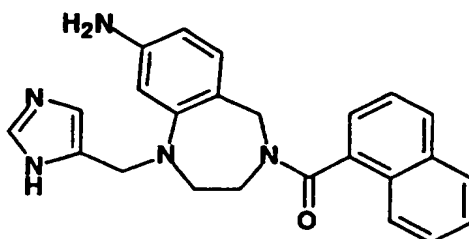
Exempl 25

5



10 **2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-8-nitro-1H-1,4-benzodiazepine, dihydrochloride.**

Sodium triacetoxymethylborohydride (0.91 g, 4.3 mmol) was added to a solution of Compound E of Example 22 (0.50 g, 1.43 mmol), 4-formyl imidazole (0.41 g, 4.3 mmol) and AcOH (4 mL) in CH₂Cl₂ (4 mL). After stirring for 15 hr, the mixture was diluted with CH₂Cl₂ (10 mL), NH₄OH (5 mL) and NaHCO₃ (5 mL), and stirred for 30 min. The layers were separated and the aqueous layer was reextracted with CH₂Cl₂ (2 x 50 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated. The product was purified over silica gel column eluting with 19/1 CHCl₃/CH₃OH to afford Example 25 (0.52 g, 85 %) as a light yellow solid. (Example 25 is also Compound F of Example 22.) MS (M+H)⁺ 428.

Example 26

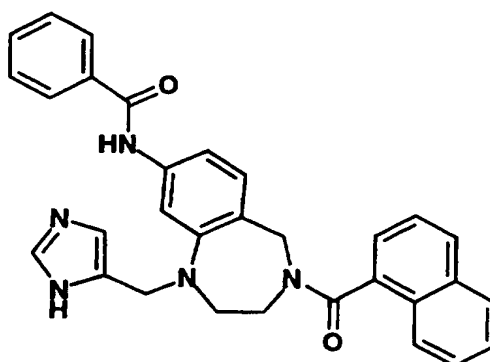
5 **2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-8-amino-1H-1,4-benzodiazepine, dihydrochloride.**

10 16 % aqueous TiCl_3 (2 mL) was added to a solution of Example 25 (0.10 g, 0.23 mmol) in $\text{AcOH}/\text{H}_2\text{O}$ (2 mL, 1:1). After stirring for 15 min, the reaction was made basic with 1N NaOH and NaHCO_3 and stirred for 30 min. The layers were separated and the aqueous layer was reextracted with $\text{CHCl}_3/\text{CH}_3\text{OH}$ (9 / 1). The combined organic layers were dried over MgSO_4 , filtered and concentrated to afford 0.92 g. (73 %) of Example 26. A

15 20 mg. sample of this material was treated with 1M HCl in ether (2 mL). A light yellow solid was formed which was triturated several times with ether and dried under vacuum to afford Example 26 (23 mg.) as a light yellow solid. (Example 26 is also Compound G of Example 22.)

MS $(\text{M}+\text{H})^+$ 398.

20

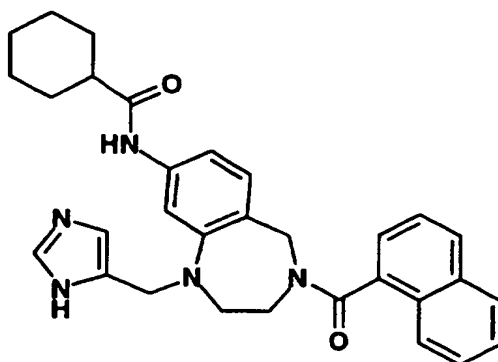
Example 27

5 **N-[2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepin-8-yl]benzamide, dihydrochloride.**

10 Benzoyl chloride (0.016 g, 0.013 mL) was added to a solution of Example 26 (0.042 g, 0.10 mmol) in CH₂Cl₂ (1 mL) and triethyl amine (0.01 g, 0.016 mL) at 0°C. After stirring for 2 hr, the mixture was diluted with NaHCO₃ (2 mL) and CHCl₃ (10 mL). The layers were separated and the aqueous layer was reextracted with CHCl₃ (2 x 20 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated. The residue was purified on a
15 silica flash column eluting with CH₃Cl/CH₃OH (9 / 1). The product was treated with 1M HCl in ether (2 mL). A light yellow solid was formed which was triturated several times with ether and dried under vacuum to afford Example 27 as a light yellow solid (0.015 g, 28%).

MS (M+H)⁺ 502.

20 IR: (KBr): 3434, 2930, 1611, 1508, 1424, 1263 cm⁻¹.

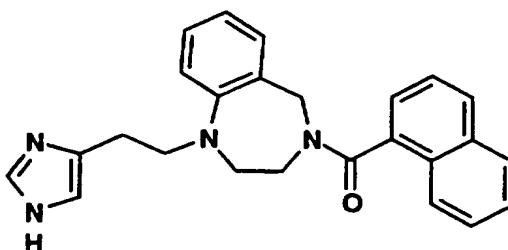
Example 28

- 5 **N-[2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepin-8-yl]cyclohexanamide, dihydrochloride.**

10 Example 28 was prepared from Example 26 and cyclohexanecarbonyl chloride as described for Example 27. The crude product was directly treated with HCl / ether. The yellow solid which formed was triturated with ether several times and dried under vacuum to afford Example 28 as a yellow solid in 90% yield.

MS (M+H)⁺ 508.

15 IR: (KBr): 3434, 2930, 1611, 1508, 1424, 1263 cm⁻¹.

Exempl 29

5 **2,3,4,5-Tetrahydro-1-[2-(1H-imidazol-4-yl)ethyl]-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, dihydrochlorid .**

10 **A. 2,3,4,5-Tetrahydro-1-[1-oxo-2-(1-triphenylmethyl-imidazol-4-yl)ethyl]-4-[(1,1-dimethylethoxy)-carbonyl]-1H-1,4-benzodiazepine**

To a solution of 250 mg (0.68 mmol) of N-triphenylmethyl-4-imidazole acetic acid and 94 μ l (0.68 mmol) of triethylamine in 3 mL of THF at -30°C under argon was added dropwise 97 μ l (0.75 mmol) of isobutylchloroformate. Stirring was continued for 10 min and a solution of 253 mg (1.02 mmol) of
15 Compound A of Example 4 in 1 mL of THF was added. The mixture was stirred 7 hours as it warmed to room temperature and diluted with ethyl acetate. The solution was washed with brine, saturated NaHCO₃ and brine, dried (MgSO₄) and concentrated. The resulting oil was subjected to flash chromatography (silica gel, 75 % ethyl acetate:hexanes) to afford 195 mg
20 (0.33 mmol, 48%) of Compound A as a white foamy solid.

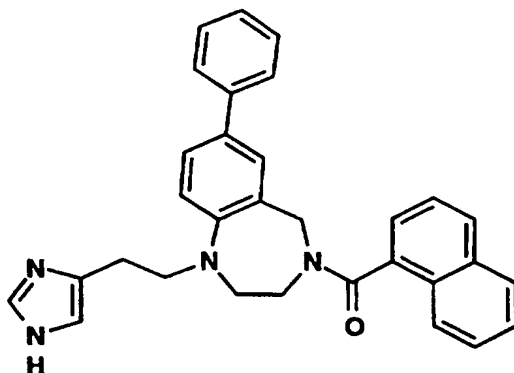
B. 2,3,4,5-Tetrahydro-1-[2-(1H-imidazol-4-yl)ethyl]-4-[(1,1-dimethylethoxy)-carbonyl]-1H-1,4-benzodiazepine

To a solution of 100 mg (0.17 mmol) of Compound A in 1 mL of THF
25 under argon was added 1 mL (1 mmol) of 1 M borane in THF. After the initial foaming had ceased, the mixture was heated at 60°C for 1 hour and cooled to room temperature. Conc. HCl (0.5 mL) was added and the solution was heated at 60°C for 1 hour and evaporated to dryness. The residue was
30 diluted with water and the solution was washed twice with ethyl acetate, rendered alkaline by the dropwise addition of 40% KOH-water, and extracted with methylene chloride (3x). The combined methylene chloride extracts were washed with brine (2x), dried (MgSO₄), and the solvent removed to give 39 mg of viscous oil. This material was subjected to flash

chromatography (silica gel, CHCl_3 :MeOH: NH_4OH 80:20:2) to afford 16 mg (0.066 mmol, 40%) of Compound B as an oil

- C. 2,3,4,5-Tetrahydro-1-[2-(1H-imidazol-4-yl)ethyl]-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, dihydrochloride.**
- Compound C was prepared from Compound B (30 mg, 0.12 mmol) as described for Compound C of Example 23 with stirring for 18 hours. The mixture was evaporated to dryness and the residue subjected to flash chromatography (silica gel, 10% methanol:chloroform) to afford 33 mg of material which was subjected to prep HPLC on a YMC S5 ODS (30x250 mm) column. Gradient elution from 30 to 100% solvent B (A: 10% methanol:water + 0.1% TFA, B: 10% water:methanol + 0.1% TFA) afforded a clear glass residue which was converted to the HCl salt by treatment with HCl-MeOH to give 20 mg (0.04 mmol, 36%) of Example 29 as a solid foam.
- MS (M+H)⁺ 397
Analysis calculated for $\text{C}_{25}\text{H}_{24}\text{N}_4\text{O} \cdot 2 \text{HCl} \cdot 1.5 \text{H}_2\text{O}$
Calc'd: C, 60.48 H, 5.89; N, 11.28.
Found: C, 60.69 H, 5.63; N, 11.12.

20

Example 30

25

2,3,4,5-Tetrahydro-1-[2-(1H-imidazol-4-yl)ethyl]-4-(1-naphthalenylcarbonyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride.

A. 2,3,4,5-tetrahydro-4-[(1,1-dimethylethoxy)-carbonyl]-7-phenyl-1H-1,4-benzodiazepin

Di-tert-butyl dicarbonate (6.1 g, 28 mmol) was added to a solution of Compound B of Example 12 (5.2 g, 23 mmol) in THF (50 mL). The mixture was stirred at room temperature for 2 hours and concentrated under vacuum. The residue was purified by flash chromatography (silica, ethyl acetate) to afford Compound A (5.7 gm, 91%) as an oil. MS: (M+H)⁺ 325

B. 2,3,4,5-Tetrahydro-1-[2-(1H-imidazol-4-yl)ethyl]-4-(1-naphthalenylcarbonyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride

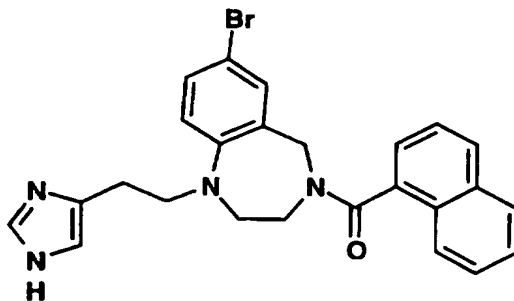
Example 30 was prepared from Compound A by the following 3 step procedure: Compound A of Example 29; Compound B of Example 29, with refluxing for 4 hours and quenching of excess borane by the dropwise addition of methanol; Compound B of Example 3, with stirring at room temperature for 2 hours and flash chromatography on silica with 10% methanol/chloroform followed by preparative HPLC (YMC S5 ODS (30x250 mm) column; gradient elution from 40 to 100% solvent B (A: 10% methanol:water + 0.1% TFA, B: 10% water:methanol + 0.1% TFA); the clear glassy residue which was converted to the HCl salt by treatment with HCl-MeOH to give Example 30 as a foamy solid.

MS (M+H)⁺ 473

Analysis calculated for C₃₁H₂₈N₄O • 2.15 HCl • 1 H₂O

Calc'd: C, 65.44 H, 5.69; N, 9.85

Found: C, 65.56 H, 5.26; N, 9.40.

Example 31

- 5 **7-Bromo-2,3,4,5-tetrahydro-1-[2-(1H-imidazol-4-yl)ethyl]-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, dihydrochloride.**

Example 31 was prepared from 7-bromo-1,4-benzodiazepine (prepared as described in Compound B of Example 11) by the following procedure:

- 10 Compound A of Example 4; Compound A of Example 29 with stirring for 2 hours and chromatography in ethyl acetate; Compound B of Example 29, with the borane reduction refluxed for 3 hours, the HCl treatment at 60°C for 2 hours, and chromatography with chloroform:methanol:NH₄OH (90:10:1);
15 Compound C of Example 23, with silica gel chromatography using 20% methanol:chloroform and preparative HPLC using a 40-100% B gradient.

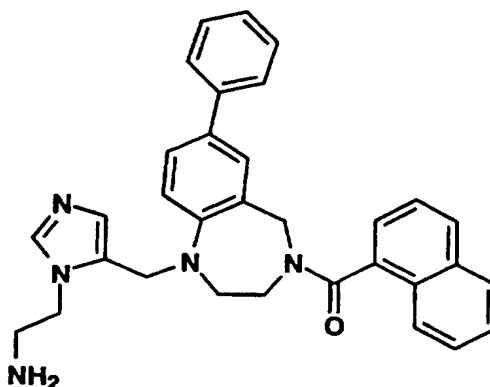
MS (M+H)⁺ 475

Analysis calculated for C₂₅H₂₃N₄OBr • 2 HCl • 0.35 H₂O

Calc'd: C, 55.41 H, 4.67; N, 9.79.

Found: C, 55.55 H, 4.53; N, 10.00.

20

Exempl 32

5 **1-[[1-(2-Aminoethyl)-1H-imidazol-5-yl]methyl]-2,3,4,5-tetrahydro-4-(1-naphthalenylcarbonyl)-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride.**

10 **A. 1-[[1-[(1,1-dimethylethoxy)-carbonyl]-1H-imidazol-4-yl]methyl]-2,3,4,5-tetrahydro-4-(1-naphthalenylcarbonyl)-7-phenyl-1H-1,4-benzodiazepine**

15 A solution of 150 mg (0.33 mmol) of Example 12, 144 mg (0.66 mmol) of di-*t*-butyldicarbonate, and 5 mg of dimethylaminopyridine in 2 mL of methylene chloride was stirred overnight under argon. The mixture, without
workup, was subjected to flash chromatography (silica gel, 50 % ethyl acetate-hexanes) afforded 142 mg (0.25 mmol, 77 %) of Compound A as a white foamy solid.

20 **B. 1-[[1-(2-(N-phthalimidoethyl)-1H-imidazol-5-yl]methyl]-2,3,4,5-tetrahydro-4-(1-naphthalenylcarbonyl)-7-phenyl-1H-1,4-benzodiazepine**

25 To an ice cooled solution, under argon, of 0.5 g (2.6 mmol) of N-hydroxyethyl-phthalimide and 315 μ L (3.9 mmol) of pyridine in 5 mL of methylene chloride was added dropwise a solution of 527 μ L (3.1 mmol) of triflic anhydride in 5 mL of methylene chloride. Stirring was continued with cooling for 0.5 hours, and at room temperature for 1 hour. A voluminous precipitate was obtained. The reaction was hydrolyzed by the addition of ice and stirred 10 minutes. The organic layer was washed with 5% NaHSO₄ and brine, dried (MgSO₄), and the solvent removed to afford 615 mg (1.9
30 mmol, 73%) of the triflate as a white solid. A solution of 44 mg (0.13 mmol)

of this triflate and 75 mg (0.13 mmol) of Compound A in 1.5 mL of methylene chloride was stirred overnight under argon. The mixture, without workup, was subjected to flash chromatography (silica gel, ethyl acetate, followed by 10% methanol-chloroform) to afford 41 mg (0.065 mmol, 50 %) of Compound B as a white foamy solid.

C. 1-[[1-(2-Aminoethyl)-1H-imidazol-5-yl]methyl]-2,3,4,5-tetrahydro-4-(1-naphthalenylcarbonyl)-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride.

A solution of 60 mg (0.095 mmol) of Compound C and 100 μ L of hydrazine in 0.5 mL of methanol was stirred overnight under argon. The resulting precipitate was removed by filtration and the clear, colorless filtrate subjected to prep HPLC on a YMC S5 ODS (30x250 mm) column. Gradient elution from 25 to 100% solvent B (A: 10% methanol:water + 0.1% TFA, B: 10% water:methanol + 0.1% TFA) afforded a white solid which was converted to the HCl salt by treatment with HCl-MeOH to give 11 mg (0.18 mmol, 19 %) of Example 32 as an amorphous pale-yellow solid.

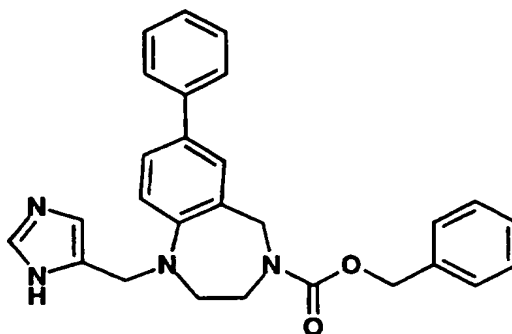
MS (M+H)⁺ 502

¹H NMR (270 MHz, CD₃OD, as a mixture of rotamers/conformers): δ 3.00 (1H, m), 3.43 (2H, m), 3.57 (2H, m), 4.09 (1H, m), 4.20 (1H, m), 4.50 (1H, m), 4.59 (1H, m), 4.72 (2H, m), 5.02 (1H, m), 6.09 (1H, s), 7.03 (1H, m), 7.22-8.05 (13H, m), 9.12 and 9.18 (1H, m).

IR (KBr): 764 cm⁻¹, 781, 1144, 1487, 1510, 1609, 2924, 3418.

25

Example 33



2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine-4-carboxylic acid, phenylmethyl ester.

A. 2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine

Sodium triacetoxyborohydride (4.5 g, 21 mmol) was added to a solution of Compound A of Example 30 (4.6 g, 14 mmol) and 4-formylimidazole (2.7 g, 28 mmol) in 1:1 methylene chloride/ AcOH (40 mL) at room temperature. The mixture was stirred at room temperature for 16 hours and concentrated under vacuum. The residue was dissolved in methylene chloride (100 mL) and 1/1 1N NaOH/ NH₄OH (100 mL) and the mixture was stirred at room temperature for 16 hours. The organic layer was separated and the aqueous layer was extracted with methylene chloride (3X50 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under vacuum. The residue was purified by flash chromatography (19/1 CHCl₃/MeOH) to afford Compound A (5.7 g, 100%) as a solid. MS: (M+H)⁺ 405

B. 2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine

Anhydrous HCl (4M, 20 mL, 80 mmol) in dioxane was added to Compound A (2.0 g, 5.0 mmol). The mixture was stirred at room temperature for 4 hours and concentrated under vacuum. The residue was dissolved in water (10 mL) and 1N NaOH (15 mL) was added. The solution was extracted with methylene chloride (4x75 mL) and the combined organic extracts were dried (MgSO₄), filtered and concentrated under vacuum to afford Compound B (1.45 g, 97%) as a solid. MS: (M+H)⁺ 305

C. 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine-4-carboxylic acid, phenylmethyl ester

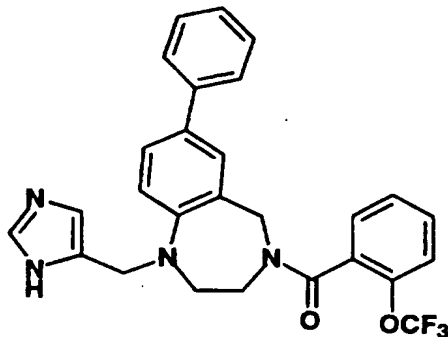
p-Nitrophenylbenzylcarbonate (0.04 g, 0.16 mmol) was added to a solution of Compound B (0.2 M, 1.0 ml, 0.16 mmol) in DMF. The mixture was stirred at room temperature for 3 hours, diluted with ethyl acetate (50 mL) and washed with 10% LiCl (50 mL). The aqueous layer was reextracted with ethyl acetate (2x50 mL). The organic fractions were combined, washed with 10% LiCl (2x50 mL), dried (MgSO₄), filtered and concentrated under vacuum. The residue was purified by flash chromatography (19/1/0.05 CHCl₃/MeOH/AcOH) to afford Example 33 (0.07 g, 93%) as a white solid. MS (M+H)⁺ 439.
Analysis calculated for C₂₇H₂₆N₄O₂ • 0.05 H₂O.

Calc'd: C, 72.52; H, 6.08; N, 12.53.

Found: C, 72.51; H, 5.85; N, 12.47.

Example 34

5



2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-[2-(trifluoromethoxy)benzoyl]-1H-1,4-benzodiazepine.

10

A solution of HOAt (0.014 gm, 0.10 mmol) in DMF (0.5 mL) was added to o-trifluoromethoxybenzoic acid (0.021 g, 0.10 mmol) at room temperature. A DMF solution of Compound B of Example 33 (0.2 M, 0.50 ml, 0.16 mmol) and diisopropyl carbodiimide (DIC, 0.013 ml, 0.10 mmol, 1.0 equiv) were added to the mixture, which was stirred at room temperature for 16 hours. The mixture was purified by ion exchange chromatography on a solid phase extraction cartridge using the following protocol:

15

1) Conditioned a Varian solid phase extraction column (1.5 g, SCX cation exchange) with 10 mL of MeOH/CH₂Cl₂

20

2) Loaded mixture onto column using a 10 mL syringe to pressurize the system

3) Wash column with 3 X 7.5 mL MeOH/CH₂Cl₂ (1:1)

4) Wash the column with 1 X 7.5 mL of 0.01 N ammonia in MeOH

25

5) Eluted column with 7.5 mL of 1.0 N ammonia in MeOH and collect into a tared receiving tube.

The solution containing product was concentrated on a Savant Speed Vac (approx. 2mm Hg for 20 hours). The residue was dissolved in CH₃CN (1 mL) and water (1 mL) and lyophilized to afford Example 34 (0.42 gm, 85%) as a white lyophilate.

30

MS: (M+H)⁺ 493

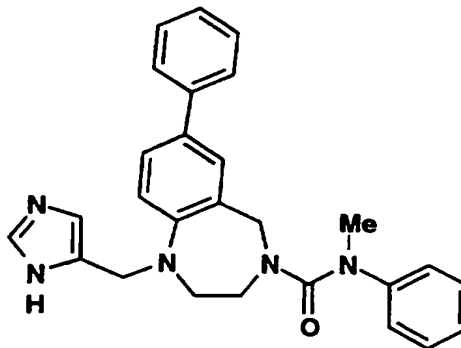
Analysis calculated for C₂₇H₂₃N₄O₂F₃ • 0.68 H₂O.

Calc'd: C, 64.25; H, 4.86; N, 11.29.

Found: C, 64.24; H, 4.83; N, 11.40.

Example 35

5



10 **1,2,3,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-N-methyl-N,7-diphenyl-4H-1,4-benzodiazepine-4-carboxamide, dihydrochloride.**

A. 7-Phenyl-1,2,3,5-tetrahydro-N-methyl-N-phenyl-4H-1,4-benzodiazepine-4-carboxamide

15 A solution of 94 mg (0.55 mmol) of N-methyl-N-phenylcarbamyl chloride in 1.5 mL of CH₂Cl₂ was added over 3 min. to a stirred mixture of 115 mg (0.5 mmol) of Compound B of Example 12 in 3 mL of CH₂Cl₂ and 2.5 mL of 1 N NaOH at 0°C. After 1.5 h the reaction was diluted with CH₂Cl₂ and water and partitioned. The aqueous layer was extracted with CH₂Cl₂ (2x) and the combined organic layers were dried (Na₂SO₄) and concentrated to give 177 mg (99%) of Compound A as a glassy residue.

20

B. 1,2,3,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-N-methyl-N,7-diphenyl-4H-1,4-benzodiazepine-4-carboxamide, dihydrochloride

25 Example 35 was prepared from Compound A as described for Compound D of Example 1. Chromatography (silica, 7% methanol, 0.5% ammonium hydroxide, 93% methylene chloride) followed by conversion to the hydrochloride salt provided Example 35 as a powder, m.p. 97-102°C. MS: (M+H)⁺ 438⁺

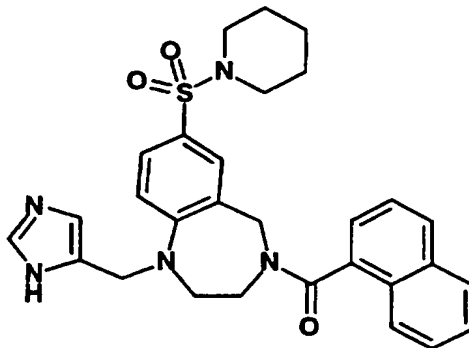
30 Analysis calculated for C₂₇H₂₇N₅O • 1.2 HCl • 0.75 H₂O • 0.25 C₄H₁₀O.

Calc'd: C, 65.51; H, 6.32; N, 13.64; Cl, 8.29.

Found: C, 65.55; H, 5.98; N, 13.50; Cl, 8.42.

Example 36

5



2,3,4,5,-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenyl-carbonyl)-7-(1-piperidinylsulfonyl)-1H-1,4-benzodiazepine, monohydrochloride.

10

A. 2,3,4,5,-Tetrahydro-7-(1-piperidinylsulfonyl)-1H-1,4-benzodiazepin-2,5-dione

A stirred solution of Compound A of Example 1 (400 mg, 2.3 mmol) in 10 mL of chlorosulfuric acid was heated at 100°C for 6 h. The solution was poured into ice-water. The aqueous suspension was extracted with ethyl acetate. The combined organic extracts were dried and filtered. The filtrate was mixed with piperidine (0.2 mL) at 0°C. The reaction was allowed to proceed for 30 min. The resultant solution was washed with 10% HCl, sat. NH₄Cl solution, dried and concentrated. The residue was triturated with ether to give Compound A as a white solid (250 mg, 34%). (M-H)⁺ 322.

15

B. 2,3,4,5,-Tetrahydro-7-(1-piperidinylsulfonyl)-1H-1,4-benzodiazepine

To a stirred suspension of LAH (200 mg, 5 mmol) in glyme was added the Compound A portionwise (185 mg, 0.57 mmol). After completion of the addition, the mixture was heated at 80°C under argon for 4h. The mixture was cooled to 0°C and ethyl acetate (20 mL) and NH₄OH (0.3 mL) solution were added successively. The mixture was allowed to stir at room temperature for 18h. The resultant suspension was filtered. The filtrate was concentrated to give Compound B as an oil (90 mg, 53%). (M-H)⁺ 295

25

30

C. 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-7-(1-pyridinylsulfonyl)-1H-1,4-benzodiazepine, monohydrochloride

Example 36 was prepared from Compound B using the 2 step procedure of Compound C of Example 2 followed by Compound D of Example 1.

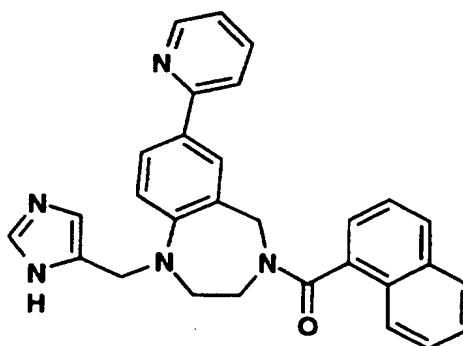
MS: (M+H)⁺ 530⁺

Analysis calculated for C₂₉H₃₁N₅O₃S • 1.1 HCl • 0.2 toluene • 0.5 C₄H₁₀O.

Calc'd: C, 62.22; H, 6.27; N, 11.20; S, 5.13; Cl, 6.23.

Found: C, 62.38; H, 6.45; N, 11.18; S, 5.23; Cl, 6.29

Example 37



2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-7-pyridin-2-yl-1H-1,4-benzodiazepine, trihydrochloride

A. 2,3,4,5-Tetrahydro-1-(1-triphenylmethyl-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-7-bromo-1H-1,4-benzodiazepine

Triphenylmethylchloride (6.83 mmol, 1.9 g) was added to a solution of Example 11 (6.83 mmol, 3.15 g) and triethylamine (34 mmol, 4.7 mL) in acetonitrile (100 mL) and the reaction was stirred for 2 hr. The resulting homogeneous yellow solution was concentrated under reduced pressure and purified by flash chromatography to give 3.9 g (81%) of Compound A as a white solid. MS (M+H)⁺ 703.

B. 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-7-pyridin-2-yl-1,4-benzodiazepine, trihydrochloride .

- 5 A mixture of Compound A (0.28 mmol, 200 mg), 2-(*tri-n*-butylstannyl) pyridine (1.4 mmol, 520 mg) and Pd(PPh₃)₄ (40 mg, 0.034 mmol) in degassed THF (3 mL) was heated to 75°C for 18 hr. The reaction was cooled to room temperature, diluted with 30 mL of MeOH and treated with 2.0 mL of TFA. The mixture was stirred for 12 hr, concentrated, purified by
10 preparative HPLC and converted to the HCl salt to give 46 mg (30% for two steps) of Example 37 as a yellow solid.

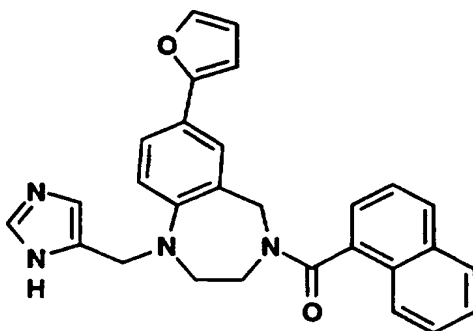
MS: (M+H)⁺ 460⁺

Analysis calculated for C₂₉H₂₅N₅O •3.09 HCl.

Calc'd: C, 60.07; H, 4.95; N, 12.24.

- 15 Found: C, 60.72; H, 5.09; N, 12.16

Example 38

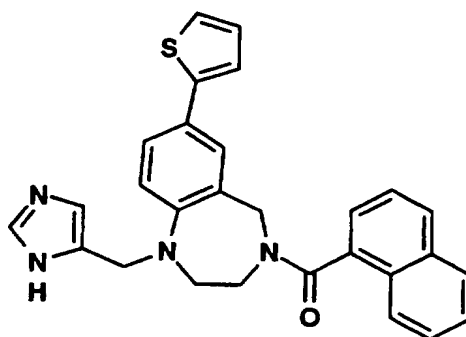


20

7-(2-Furanyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, dihydrochloride.

- Example 38 was prepared as a green solid in 11% yield from Compound A
25 of Example 37 and 2-(tributylstannyl)furan as described for Compound B of Example 37.

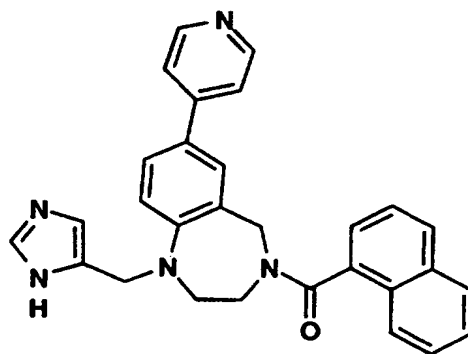
MS: (M+H)⁺ 449⁺

Example 39

- 5 **2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-7-(2-thienyl)-1H-1,4-benzodiazepine, dihydrochloride.**

10 Example 39 was prepared as a green solid in 10% yield from Compound A of Example 37 and 2-(tributylstannyl)thiophene as described for Compound B of Example 37.

MS: (M+H)⁺ 465

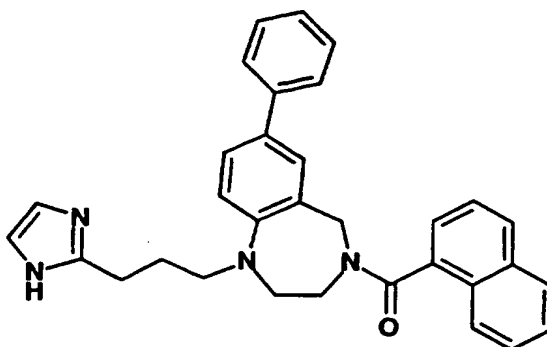
Example 40

- 15
- 20 **2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-pyridinyl)-7-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, trihydrochloride.**

Trifluoroacetic anhydride (0.4 mmol, 60 mL) was added to a solution of 2,3,4,5-tetrahydro-4-(1-naphthalenylcarbonyl)-7-bromo-1H-1,4-benzodiazepine (prepared as described in Example 11, 0.26 mmol, 100 mg)

and NEt_3 (1.04 mmol, 150 mL) in CH_2Cl_2 (5 mL) and the homogeneous, colorless solution was maintained at room temperature for 1 hr. The reaction was concentrated, and the residue passed through a short silica gel column (gradient elution: 30% ethyl acetate/hexanes to neat ethyl acetate) to isolate a fluffy white solid which was taken to next step without further purification. This material was dissolved in toluene (2.0 mL) together with 4-(tributylstannyl)pyridine (0.52 mmol, 190 mg) and $\text{Pd}(\text{PPh}_3)_4$ (30 mg, 0.026 mmol) and the solution was purged with argon for 15 minutes. The homogeneous brown solution was heated to 115°C for 20 hrs to give a black heterogeneous solution. The reaction was concentrated and redissolved in $\text{MeOH}/2\text{N NaOH}$ (aq) (5 mL:5mL) and stirred at room temperature for 30 minutes. MeOH was removed under reduced pressure and the reaction was partitioned between 10% isopropanol/ CH_2Cl_2 and 2N NaOH /saturated NaCl (1:1, 10 mL) and extracted 2x with 10% isopropanol/ CH_2Cl_2 (2X5mL). The pooled organic phase was dried over Na_2SO_4 , concentrated and passed through a short silica gel column (eluted with 95:5:1, CHCl_3 : MeOH : TEA) to remove polar impurities. The crude material was taken-up in 1,2-dichloroethane: AcOH (1:1, 2 mL total) and treated with 4-formyl imidazole (62 mg, 0.65 mmol) and $\text{NaBH}(\text{OAc})_3$ (0.78 mmol, 165 mg) and the solution was heated to 55°C for 2 hrs. The reaction was concentrated, partitioned between 10% isopropanol/ CH_2Cl_2 and 2N NaOH /saturated NaCl (1:1, 10 mL) and extracted 2x with 10% isopropanol/ CH_2Cl_2 (2X5mL). The pooled organic phase was concentrated, dissolved in MeOH/TFA (5 mL: 0.5 mL) and purified by prep HPLC (YMC S5 ODS 30 X 250 mm: R_t = 19-21 min; gradient elution with 0 to 100% buffer B over 30 min; Buffer A = $\text{MeOH}:\text{H}_2\text{O}:\text{TFA}$ (10:90:0.1); Buffer B = $\text{MeOH}:\text{H}_2\text{O}:\text{TFA}$ (90:10:0.1); 25 mL/min). The trifluoroacetate salt was converted to the HCl salt by lyophilizing in 1M HCl (2X5mL) to give 75 mg (50% yield over 4 steps) of Example 40 as a bright yellow solid

MS: $(\text{M}+\text{H})^+$ 460

Exempl 41

5 **2,3,4,5-Tetrahydro-1-[3-(1H-imidazol-2-yl)propyl]-4-(1-naphthalenylcarbonyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride.**

A. **3-[Imidazol-2-yl]-propenoic acid, ethyl ester.**

10 To a cooled (0°C) solution of sodium hydride (1.86g, 45.8 mmol, 60% dispersion in mineral oil, prewashed with THF and dried over N₂) in 1,2-dimethoxyethane (DME, 20 mL) was added triethylphosphonoacetate (12g, 54.1 mmol) dissolved in DME (10 mL) dropwise over 15 minutes. The solution was stirred for 1 hr at ambient temperature followed by the addition
15 of 2-imidazole acetaldehyde (4 g, 41.6 mmol) in 20 mL of DME. The solution was stirred and heated to reflux (85°C) for 15 minutes followed by cooling to 60°C for 1 hr. On cooling, the solution was concentrated to 1/2 volume and filtered. The solid was recrystallized from methanol/ethyl acetate/hexanes to give 5.1g (74%) of Compound A as a white crystalline solid. MS (M+H)⁺
20 167⁺.

B. **3-[Imidazol-2-yl]-propanoic acid, ethyl ester**

A solution of Compound A (4.01g, 24.2 mmol) in absolute ethanol (100 mL, heated to dissolve) was hydrogenated using Pd/C (0.5g) at
25 ambient temperature for 16 hr. Following removal of H₂ under vacuum, the catalyst was removed by filtration through a bed of celite. The filtrate was concentrated under vacuum to give 4.0 g (100%) of Compound B as a white crystalline solid. MS (M+H)⁺ 169⁺.

30

C. 3-[N-Triphenylmethyl-imidazol-2-yl]-propanoic acid, thyl ester

Compound B was prepared from Compound A as described for Compound A of Example 6, using methylene chloride as solvent and triethylamine as base. After aqueous workup, recrystallization from ethyl acetate/hexanes afforded Compound B as a white microcrystalline solid. MS (M+H)⁺ 411⁺.

D. 3-[N-Triphenylmethyl-imidazol-2-yl]-propan-1-ol

A solution of Compound C (0.80g, 1.95 mmol) in THF (15 mL) was cooled to 0°C under argon and a 1M solution of lithium aluminum hydride (2 mL, 2 mmol) was added dropwise with stirring. The reaction was stirred at ambient temperature for 16 hr. Water (2 mL) was added slowly and the solution was concentrated. Water (40 mL) and ethyl ether (60 mL) were added and the layers were separated. The ether layer was dried (MgSO₄) and concentrated. The residue was chromatographed (flash silica, 10:1 methylene chloride:methanol). Fractions containing product were pooled and concentrated to give 680 mg (95%) of Compound D as a white crystalline solid. MS (M+H)⁺.

E. 3-[N-Triphenylmethyl-imidazol-2-yl]-propanal

A solution of oxalyl chloride (0.3 mL, 0.6 mmol) in 2 mL methylene chloride was cooled to -63°C under argon. DMSO (0.056mL, 0.8 mmol) in methylene chloride (0.5 mL) was added over 10 min followed by addition of Compound D (147 mg, 0.4 mmol) in methylene chloride (6 mL) over 15 min keeping the reaction temperature below -50°C. The resulting clear solution was stirred for 50 min at -63°C. A solution of triethylamine (0.25 mL, 1.8 mmol) in methylene chloride (1 mL) was added over 15 min keeping the solution below -50°C. The mixture was stirred for 15 min followed by addition of 1M potassium hydrogen sulfate (4.5 mL), water (20 mL) and ethyl ether (60 mL). The layers were separated and the aqueous layer was made basic using half saturated aqueous sodium bicarbonate and washed with ethyl acetate (3x30 mL). The combined organic layers were dried (MgSO₄) and concentrated to yield 146 mg (>99%) of Compound E as a yellowish gum.

F. 2,3,4,5-Tetrahydro-4-(1-naphthalenylcarbonyl)-7-phenyl-1H-1,4-benzodiazepine

A solution of Compound B of Example 12 (3.5 g, 15.63 mmol) and N,N-diisopropylethylamine (2.73 mL, 15.63 mmol) in DMF (10 mL) was added at once to a stirred solution of EDC (3.0 g, 15.63 mmol), HOBt (2.1 g, 15.63 mmol) and 1-naphthoic acid (2.42 g, 14.06 mmol) in DMF (20 mL). The mixture was stirred for 4 h, poured into water (200 mL) and the product was extracted with ethyl acetate (2X100 mL). The combined ethyl acetate layers were washed with water (3X200 mL), brine (100 mL), dried (MgSO₄), concentrated and chromatographed (silica gel, 50% ethyl acetate/hexane). Fractions containing the desired compound were collected and concentrated to yield Compound A as a clear oil (4.4 g, 93%), (M+H)⁺ 379⁺.

G. 2,3,4,5-Tetrahydro-1-[3-(1-triphenylmethyl-imidazol-2-yl)propyl]-4-(1-naphthalenylcarbonyl)-7-phenyl-1H-1,4-benzodiazepine

A solution of Compound E (109 mg, 0.29 mmol) and Compound F (100 mg, 0.26 mmol) were dissolved in 1,2-dichloroethane (10 mL). Acetic acid (0.1 mL) was added followed by sodium triacetoxyborohydride (84 mg, 0.40 mmol). The mixture was stirred at 50°C for 2h. Saturated NaHCO₃ (10 mL) was added and the mixture was concentrated, partitioned between ethyl acetate (50 mL) and water (20 mL). The organic layer was separated, dried (MgSO₄), concentrated and chromatographed (silica gel, 40% ethyl acetate/hexane). Fractions containing the desired compound were collected and concentrated to yield Compound G as a clear glass (100 mg, 47%), MS (M+H)⁺ 729⁺.

H. 2,3,4,5-Tetrahydro-1-[3-(1H-imidazol-2-yl)propyl]-4-(1-naphthalenylcarbonyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride.

A solution of Compound G (70 mg, 0.096 mmol) in methylene chloride (7 mL), TFA (7 mL), and triethylsilane (0.36 mg, 0.50 mL, 0.31 mmol) was stirred for 30 min at room temperature. The mixture was concentrated and the residue was dissolved in methylene chloride (60 mL) and concentrated. This procedure was repeated five times to yield the crude product as a white sticky solid in quantitative yield. This crude solid was purified by preparative HPLC (YMC S-5 ODS-A column, 30 X 250 mm;

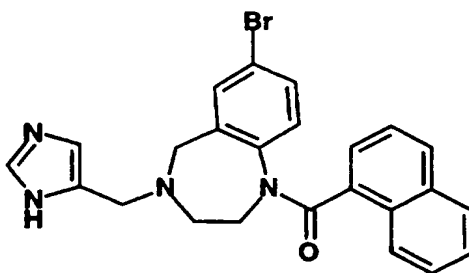
solvent A, 0.1% TFA in 90% water, 10 % methanol; solvent B, 0.1% TFA in 10% water, 90% methanol: 20-100% B in 60 min, flow rate 25 mL/min).

Fractions containing the desired product were combined, concentrated and lyophilized. This lyophilate was dissolved in methanol (0.5 mL) and 1N HCl (5mL). This mixture was concentrated and lyophilized. This procedure was repeated to provide Example 41 as a white solid (15 mg, 28%).

MS (M+H)⁺ 487⁺

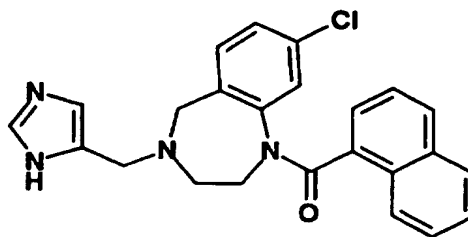
¹H-NMR (CD₃OD, 400 MHz) δ 8.05-7.00 (16H, m), 6.20 (1H, m), 4.47-4.26 (2H, dd, J=15.0), 4.17 (1H, m), 4.08 (1H, m), 3.48 (1H, m), 3.43 (1H, m), 3.33 (1H, m), 3.12 (1H, t), 3.06 (1H, t), 2.98 (1H, m), 2.16 (1H, q), 2.04 (1H, q).

Example 42



7-Bromo-2,3,4,5-tetrahydro-4-(1H-imidazol-4-ylmethyl)-1-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, dihydrochloride.

Example 42 was prepared as an off white solid from 7-bromo-1,4-benzodiazepine (prepared as described in Compound B of Example 11) using the following procedure: Compound A of Example 4; Compound B of Example 4; Compound C of Example 4; Compound D of Example 1, using methylene chloride as solvent, purification by prep HPLC (YMC S5 ODS 30 X 250 mm; gradient elution with 0 to 100% buffer B over 45 min; buffer A = MeOH:H₂O:TFA (10:90:0.1); buffer B = MeOH:H₂O:TFA (90:10:0.1); 25 mL/min) and conversion to the HCl salt by lyophilization from 1M HCl. MS (M+H⁺) 462. ¹H-NMR (CD₃OD): 3.5 (br s, 2H), 3.80 (m, 2H), 4.80 (br, 2H), 5.30 (br, 2H), 6.60 (m, 1H), 7.15-8.15 (m, 11 H), 9.10 (s, 1H).

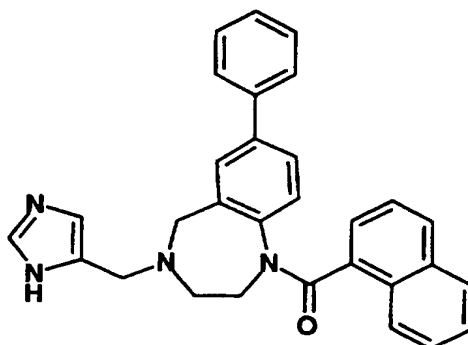
Example 43

- 5 **8-Chloro-2,3,4,5-tetrahydro-4-(1H-imidazol-4-ylmethyl)-
1-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine,
dihydrochloride.**

Example 43 was prepared as an off white solid from Compound B
10 of Example 2 as described for Example 42.
MS (M+H⁺) 459. ¹H-NMR (CD₃OD): 3.40-3.80 (br s, 4H), 4.4(br., 2H), 4.7
(br., 2H), 5.20 (br., 2H), 6.65 (d, 1H), 7.00-8.15 (m, 16 H), 9.00(s, 1H).

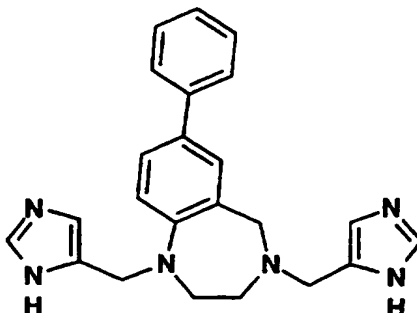
Example 44

15



- 20 **2,3,4,5-Tetrahydro-4-(1H-imidazol-4-ylmethyl)-1-(1-
naphthalenylcarbonyl)-7-phenyl-1H-1,4-benzodiazepine,
hydrochloride.**

Example 44 was prepared as an off white solid from Compound B
of Example 12 as described for Example 42.
MS (M+H⁺) 459. ¹H-NMR (CD₃OD): 3.40-3.80 (br s, 4H), 4.4(br, 2H), 4.7
25 (br, 2H), 5.20 (br, 2H), 6.65 (d, 1H), 7.00-8.15 (m, 16 H), 9.00 (s, 1H).

Example 45

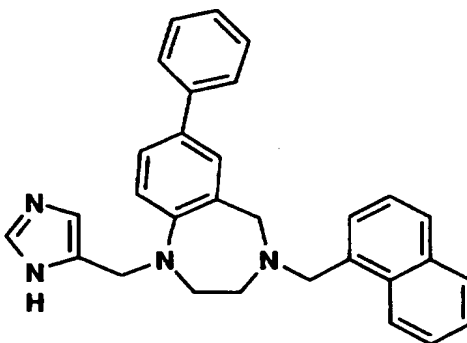
5

2,3,4,5-Tetrahydro-1,4-bis(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride.

Example 45 was prepared as an off white solid from Compound B of Example 12 as described for Compound D of Example 1, using methylene chloride as solvent, 4.3 equivalents of 4-formylimidazole, 4.3 equivalents of sodium triacetoxyborohydride and with stirring for 4 hours.

MS (M+H⁺) 385. ¹H-NMR (CD₃OD): 3.5 (br s, 4H), 4.60 (br, 2H), 4.9 (br, 4H), 7.2-8.0 (m, 10 H), 8.90 (s, 1H), 9.05 (s, 1H).

15

Example 46

2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylmethyl)-7-phenyl-1H-1,4-benzodiazepine, trifluoroacetate.

Lithium aluminum hydride (1 M in THF, 15 mL, 15 mmol) was added to a suspension of Example 12 (0.25 g, 0.55 mmol) in THF (10 mL). The suspension was refluxed for 5 hr, cooled to 0°C, and 20% aqueous NaOH (10 mL) and H₂O (10 mL) were added. The mixture was saturated with NaCl and extracted with CH₂Cl₂ (2x 50 mL). Drying over Na₂SO₄ and evaporation of the solvent gave a solid (0.21 g) which was dissolved in MeOH/TFA (10:1) and purified by prep HPLC (YMC S5 ODS 30 X 250 mm; gradient elution with 0 to 100% buffer B over 45 min; Buffer A = MeOH:H₂O:TFA (10:90:0.1); Buffer B = MeOH:H₂O:TFA (90:10:0.1); 25 mL/min) to provide Example 46 (50 mg) as an off white solid.

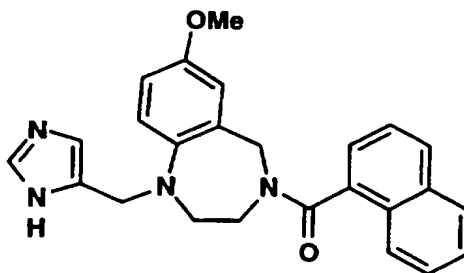
MS (M+H⁺) 445.

Analysis calculated for C₃₀H₂₈N₄O • 2 HCl • 0.3 H₂O.

Calc'd: C, 68.90; H, 5.90; N, 10.71.

Found: C, 68.94; H, 5.78; N, 10.43.

Example 47



2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-methoxy-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, dihydrochloride.

Example 47 was prepared as an off white solid from 6-hydroxy-isatoic anhydride by the following procedure: Compound A of Example 1, with refluxing for 18 hr, and washing of the precipitate with water; formation of the methyl ether by stirring with 1.3 equivalents of methyl iodide in DMF in the presence of K₂CO₃ at room temperature for 12 hrs; Compound B of Example 1, with quenching with 20% NaOH and water followed by extraction with CH₂Cl₂; Compound C of Example 2, with the product carried on without chromatography; Compound D of Example 1, using methylene chloride,

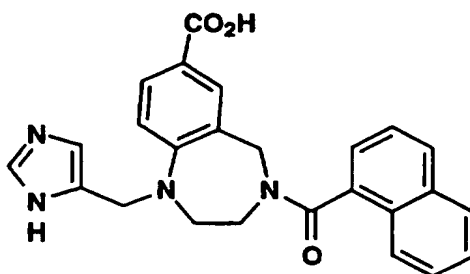
stirring for 5 hours and purification by flash chromatography (94.5:5:0.5, CH₂Cl₂:MeOH:NH₄OH) before formation of the hydrochloride salt.

Analysis calculated for C₂₄H₂₄N₄O₂ • 2 HCl • 0.61 H₂O.

Calc'd: C, 60.50; H, 5.53; N, 11.29.

5 Found: C, 60.51; H, 5.59; N, 11.14

Example 48



10

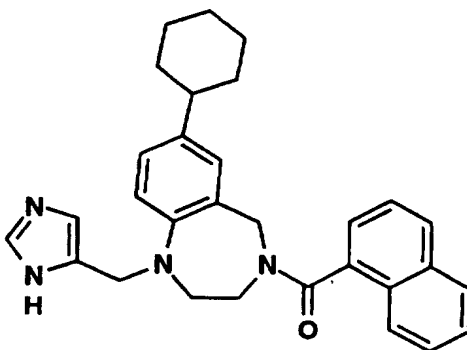
2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine-7-carboxylic acid, dihydrochloride.

15 n-BuLi (2.5 M in THF, 0.22 mL, 0.55 mmol) was added to a solution of Example 11 (0.12 g, 0.26 mmol) in THF (10 mL) at -78°C. The resulting brown solution was stirred for 4 min at -78°C, purged with CO₂ for 20 min and quenched with acetic acid/water (2:1, 2 mL). The solvent was evaporated, the residue was dissolved in methylene chloride, and the
20 solution was washed with brine, dried (Na₂SO₄) and evaporated. The residue was purified by prep HPLC (YMC S5 ODS 30 X 250 mm; gradient elution with 0 to 100% buffer B over 45 min; Buffer A = MeOH:H₂O:TFA (10:90:0.1); Buffer B = MeOH:H₂O:TFA (90:10:0.1); 25 mL/min) and the product was converted to the HCl salt by lyophilization from 1M HCl (5 mL) to
25 provide Example 48 (50 mg, 45%) as an off white solid.

MS (M+H⁺) 427.

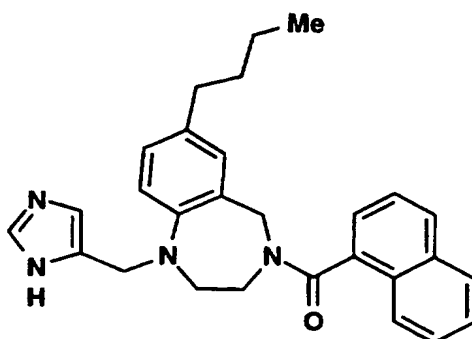
¹H-NMR (CD₃OD): 3.05 (br m, 1H), 3.20 (m, 1H), 4.00 (br s, 1H), 4.20 (br s, 1H), 4.40 (br d, 1H), 4.50 (br s, 1H), 4.65 (s, 1H), 5.05 (s, 1H), 6.60 (d, 1H), 7.19-8.20 (m, 11H), 8.85 (s, 1H), 8.95(s, 1H).

30

Example 49

5 2,3,4,5-Tetrahydro-1-(1H-imidazol-5-ylmethyl)-4-(1-naphthalenylcarbonyl)-7-cyclohexyl-1H-1,4-benzodiazepine, 2.5 hydrochloride.

- 10 n-BuLi (2.5M in THF, 1.4 mL, 3.5 mmol) was added to a solution of Example 11 (0.68 g, 1.4 mmol) in THF (15 mL) at -78°C . The resulting brown solution was stirred for 5 min. at -78°C and cyclohexanone (1.5 ml, 14.4 mmol) was added. After stirring at -78°C for 10 min., the reaction was quenched with sat. NH_4Cl (3 mL) and sat. NaHCO_3 (10 mL). The aqueous solution was extracted with CH_2Cl_2 . The organic phase was dried
- 15 (Na_2SO_4) and evaporated. The residue was purified by chromatography (silica gel, 10% CH_3OH , 0.5% AcOH in CH_2Cl_2) to give the crude alcohol (80 mg) as well as a 25% yield of Example 50. TFA (3 mL) was added to the crude alcohol (40 mg) in CH_2Cl_2 (15 mL) at -78°C . The resulting blue solution was treated with solid NaBH_4 (0.7 g, 18.5 mmol). The mixture was
- 20 warmed to room temperature and quenched with NH_4OH (10 mL). The solution was diluted with CH_2Cl_2 (20 mL) and washed with aqueous NaOH (1N, 10 mL) and brine (10 mL). Drying over Na_2SO_4 and evaporation of solvent gave a solid which was converted to its HCl salt by lyophilization from 1M HCl to provide Example 49 as a yellow solid (30 mg).
- 25 MS ($\text{M}+\text{H}^+$) 465.
 ^1H -NMR (CD_3OD): 1.50-2.40 (m, 10H), 2.89 (m, 1H), 3.20 (m, 2H), 4.00 (br s, 1H), 4.20 (br s, 1H), 4.40 (br d, 1H), 4.50 (br s, 1H), 4.65 (s, 1H), 4.95 (s, 1H), 6.15 (d, 1H), 7.19-8.10 (m, 11H), 8.85 (s, 1H), 8.95 (s, 1H).

Exempl 50

- 5 **7-Butyl-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, dihydrochloride.**

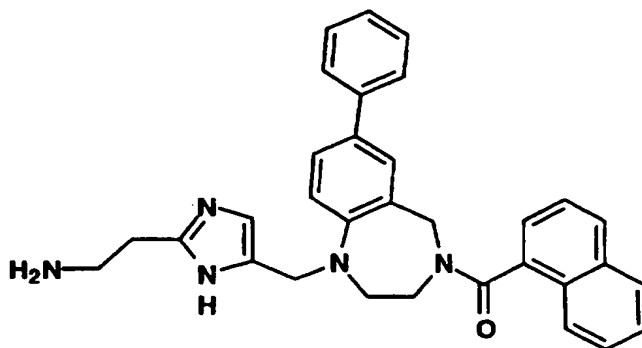
See Example 49 for the preparation of Example 50.

MS (M+H⁺) 439

- 10 ¹H-NMR (CD₃OD): 0.5-2.40 (m, 9H), 2.9 (m, 2H), 3.20 (m, 2H), 4.00 (br s, 1H), 4.20 (br s, 1H), 4.40 (br d, 1H), 4.50 (br s, 1H), 4.65 (s, 1H), 4.95 (s, 1H), 6.00 (br s, 1H), 7.19-8.10 (m, 11H), 8.85 (s, 1H), 8.95(s, 1H).

Example 51

15



- 20 **1-[[2-(2-Aminoethyl)-1H-imidazol-4-yl]methyl]-2,3,4,5-tetrahydro-4-(1-naphthalenylcarbonyl)-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride.**

Example 51 was prepared by the following 2 step procedure.
T trahydro-4-(1-naphthalenylcarbonyl)-7-phenyl-1H-1,4-benzodiazepine (prepared as described in Example 12) was reductively alkylated with

- Compound B of Example 20 as described for Compound D of Example 1, with stirring for 18 hours. Without workup, the mixture was subjected to flash chromatography (silica, 60 % ethyl acetate-hexanes) to afford the bis-Boc analog. Deprotection and purification as described in Compound C of Example 20 afforded Example 51 as an off-white powder.

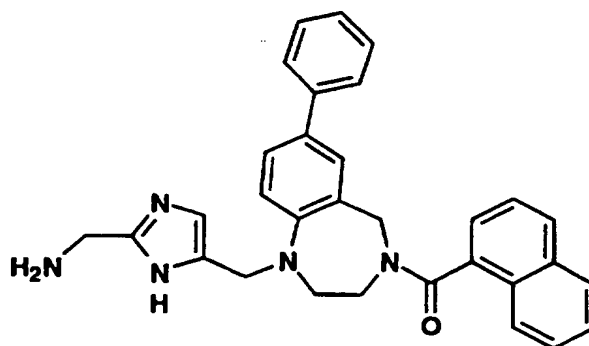
MS (M+H)⁺ 502

Analysis calculated for C₃₂H₃₁N₅O • 3 HCl • 0.5 H₂O.

Calc'd: C, 61.99; H, 5.69; N, 11.29.

Found: C, 61.68; H, 6.07; N, 11.22.

Example 52



- 1-[[2-(Aminomethyl)-1H-imidazol-4-yl]methyl]-2,3,4,5-tetrahydro-4-(1-naphthalenylcarbonyl)-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride.

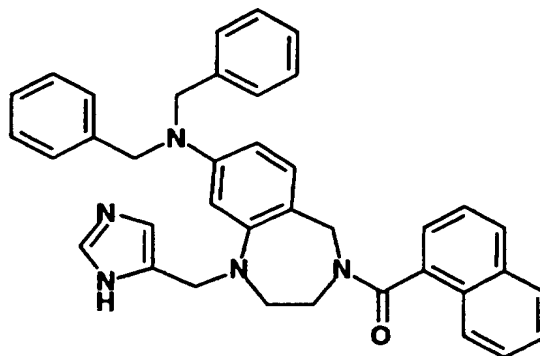
- Example 52 was prepared from tetrahydro-4-(1-naphthalenylcarbonyl)-7-phenyl-1H-1,4-benzodiazepine and [2-(2-[[[(1,1-dimethyl)-ethoxycarbonyl]amino]methyl]-1-[(1,1-dimethyl)-ethoxycarbonyl]-imidazol-4-yl]carboxaldehyde (see Example 21) as described for Example 51.

MS (M+H)⁺ 488

- Analysis calculated for C₃₁H₂₉N₅O • 3 HCl.

Calc'd: C, 62.37; H, 5.40; N, 11.73.

Found: C, 62.13 H, 5.67; N, 11.73.

Example 53

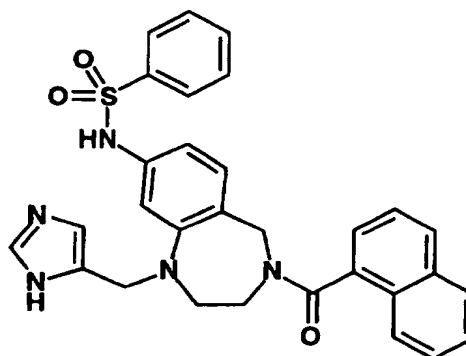
5 **2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-8-[N,N-bis(phenyl-methyl)amino]-1H-1,4-benzodiazepine, trihydrochloride.**

10 Sodium triacetoxyborohydride (0.079 g, 0.37 mmol) was added to a solution of Example 26 (0.50 g, 0.12 mmol), benzaldehyde (0.04 g, 0.37 mmol) and AcOH (1 mL) in CH₂Cl₂ (1 mL). After stirring for 16 hr, the reaction was diluted with CH₂Cl₂ (10 mL), NH₄OH (3 mL) and NaHCO₃ (3 mL), and stirred for 30 min. The layers were separated and the aqueous layer was reextracted with CH₂Cl₂ (2 x 50 mL). The combined organic

15 layers were dried over MgSO₄, filtered and concentrated. The residue was treated with HCl/ether, a yellow solid was formed which was triturated with ether several times and dried under vacuum to afford Example 53 (0.43 g, 60%).

MS (M+H)⁺ 579

20 ¹H NMR (270 MHz, CD₃OD): δ 8.8 (d, 1H, J = 20 Hz), 8.04-7.9 (m, 2H), 7.6-7.2 (m, 18 H), 7.0 (s, 0.5H), 5.87 (s, 0.5H), 4.95-4.8 (m, 5H), 4.5-4.1 (m, 3H), 3.85 (m, 1H), 3.4-3.2 (m, 2H), 3.0 (m, 1H).

Example 54

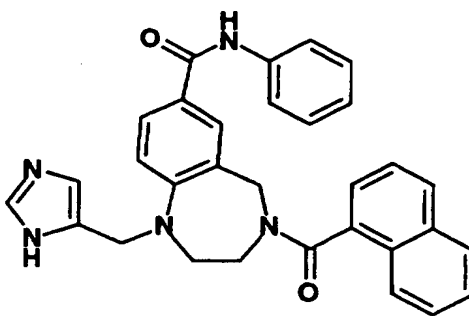
5 N-[2,3,4,5-Tetrahydro-1-(1H-imidazol-4-yl-methyl)-4-(1-naphthalenyl-carbonyl)-1H-1,4-benzodiazepin-8-yl]phenylsulfonamide, dihydrochloride.

10 Benzenesulphonamide (0.024 g, 0.13 mmol) was added to a solution of Example 26 (0.50 g, 0.12 mmol) and triethylamine (0.019 mL, 0.13mmol) in CH₂Cl₂ (1 mL). After stirring for 16 hr, the reaction was diluted with CHCl₃ (10 mL) and NaHCO₃ (3 mL) and stirred for 30 min. The layers were separated and the aqueous layer was reextracted with CHCl₃ (2 x 20

15 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated. The residue was treated with HCl/ether, a yellow solid was formed which was triturated with ether several times and dried under vacuum to afford Example 54 (0.64.2 g, 83 %) as a light brown solid.

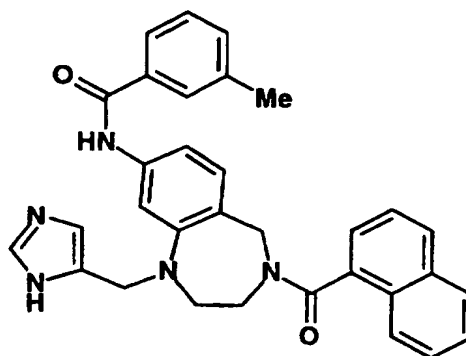
MS (M+H)⁺ 538

20 ¹H NMR (270 MHz, CD₃OD): d 8.8 (d, 1H, J = 20 Hz), 8.1-7.23 (m, 13H), 7.1 (d, 0.5H, J = 8 Hz), 7.0 (d, 0.5H, J = 8Hz), 6.9 (d, 0.5H, J = 8Hz), 6.62 (d, 0.5H, J = 8Hz), 6.12 (d, 0.5H, J = 8Hz), 5.71 (d, 0.5H, J = 8Hz) 4.55 (m, 1H), 4.55-3.9 (m, 3H), 3.45-3.25 (m, 2H), 3.0-2.8 (m, 2H).

Example 55

5 **N-Phenyl-2,3,4,5-tetrahydro-1-(1H-imidazol-4-yl-methyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine-7-carboxamide, dihydrochloride.**

10 A mixture of Example 48 (50 mg, 0.11 mmol), PyBROP (0.28 g, 0.6 mmol), DMAP (0.04 g, 0.3 mmol) and DIEA (0.3 g, 2.3 mmol) in DMF (5 mL) was stirred for 5 min, aniline (1 mL, 11 mmol) was added and the resulting homogeneous solution was stirred for two days. After removing DMF, the residue was purified by prep HPLC (YMC S5 ODS 30 X 250 mm: Rt = 22-23 min; gradient elution with 0 to 100% buffer B over 45 min; Buffer A =
15 MeOH:H₂O:TFA (10:90:0.1); Buffer B = MeOH:H₂O:TFA (90:10:0.1); 25 mL/min) and conversion to the HCl salt was accomplished by lyophilizing from 1M HCl (5 mL) to provide Example 55 (40 mg, 34%) as a yellow solid.
MS (M+H)⁺ 502
1H-NMR (CD₃OD): 3.10 (br m, 1H), 3.25 (m, 1H), 4.10 (br s, 1H), 4.25 (br s, 1H), 4.45 (br d, 1H), 4.55 (br s, 1H), 4.60 (s, 1H), 5.10 (s, 1H), 6.64 (d, 1H),
20 7.19-8.20 (m, 16H), 8.85 (s, 1H), 8.95(s, 1H).

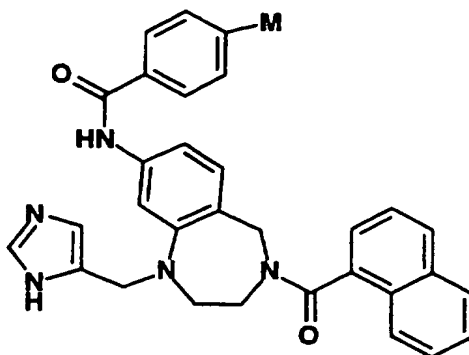
Example 56

- 5 **N-[2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepin-8-yl]-3-methylbenzamide, dihydrochloride.**

10 Example 56 was prepared from m-toluoyl chloride and Example 26 as described for Example 27, with stirring for 16 hr. The HCl salt was formed directly from the crude product to provide a 94% yield of Example 56 as a brown solid.

MS (M+H)⁺ 516

15 ¹H NMR (270 MHz, CD₃OD): δ 8.8 (d, 1H, J = 20 Hz), 8.15-7.2 (m, 14H), 6.8 (d, 0.5 H, J = 7 Hz), 5.95 (d, 0.5 H, J = 7 Hz), 4.98 (s, 1H), 4.7-4.19 (m, 3H), 4.19-3.9 (m, 1H), 3.52-3.2 (m, 1.5H), 3.25-3.15 (m, 0.5H), 3.1-2.8 (m, 1H), 2.46-2.33 (m, 3H).

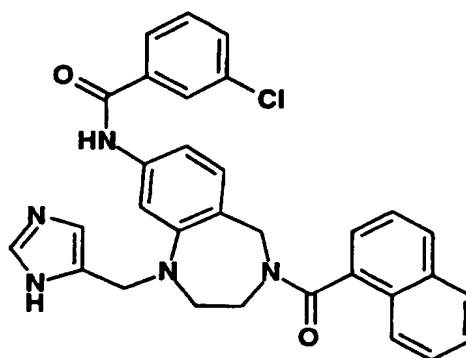
Exempl 57

- 5 **N-[2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepin-8-yl]-4-methylbenzamide, dihydrochloride.**

10 Example 57 was prepared from p-toluoyl chloride and Example 26 as described for Example 56.

MS (M+H)⁺ 516

¹H NMR (270 MHz, CD₃OD): d 8.8 (d, 1H, J = 20 Hz), 8.15-7.72 (m, 5H), 7.7-7.2 (m, 9H), 6.77 (d, 0.5H, J = 7 Hz), 5.92 (d, 0.5H, J = 7 Hz), 4.98 (s, 1H), 4.7-4.19 (m, 3H), 4.12-3.9 (m, 1H), 3.52-3.2 (m, 1.5H), 3.25-3.15 (m, 0.5H),
15 3.1-2.8 (m, 1H), 2.46-2.33 (m, 3H).

Exempl 58

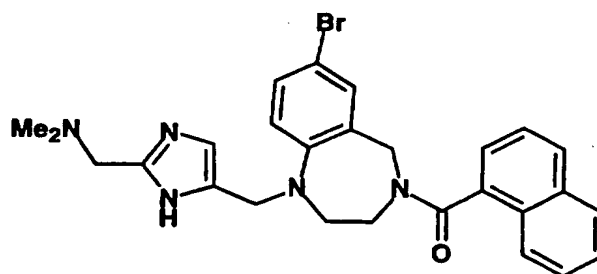
- 5 **3-Chloro-N-[2,3,4,5-tetrahydro-1-(1H-imidazol-4-yl-methyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepin-8-yl]benzamide, dihydrochloride.**

Example 58 was prepared from 3-chlorobenzoyl chloride and
 10 Example 26 as described for Example 56.

MS (M+H)⁺ 536

¹H NMR (270 MHz, CD₃OD): d 8.87 (d, 1H, J = 20 Hz), 8.05-7.82 (m, 4H),
 7.75-7.2 (m, 10H), 6.8 (d, 0.5 H, J = 8 Hz), 5.9 (d, 0.5 H, J = 8 Hz), 4.96 (s,
 1H), 4.65-3.9 (m, 4H), 3.4-3.3 (m, 2H), 3.05-2.9 (m, 1H).

15

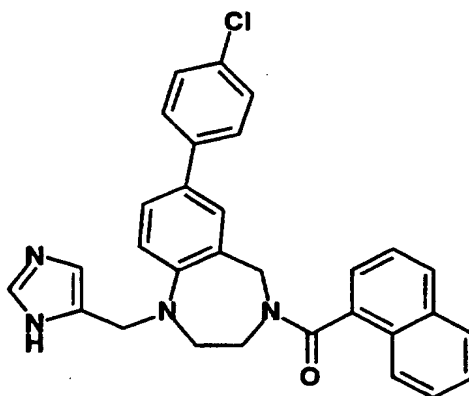
Example 59

- 20 **7-Bromo-2,3,4,5-tetrahydro-1-[[2-[(dimethylamino)-methyl]-1H-imidazol-4-yl]methyl]-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, dihydrochloride.**

A stirred suspension of Example 11 (100 mg, 0.22 mmol),
 25 paraformaldehyde (10 mg, 0.33 mmol) and dimethylamine (40% in water,

0.041 mL) in acetic acid was heated at 90°C for 18 h. The mixture was partitioned between ethyl acetate and sat. NaHCO₃ solution. The organic layer was separated, dried and concentrated in vacuo. The residue was purified by flash chromatography (30% MeOH, 69% ethyl acetate and 1% NH₄OH) to give a solid which was dissolved in methanol. 1N HCl in ether was added, and the solvent removed to give Example 59 as a yellow solid (30 mg, 23%).
MS (M+H)⁺ 518

10

Example 60

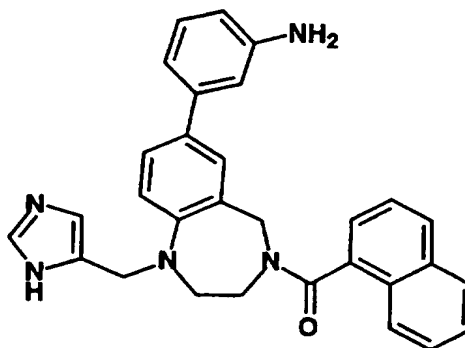
15

7-(4-Chlorophenyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, dihydrochloride.

A solution of Compound A of Example 37 (0.142 g, 0.2 mmol) in DMF (5 mL) and THF (10 mL) was degassed for 5 min with argon. Tetrakis(triphenylphosphine)palladium (0.10 g, 0.08 mmol) was added and the solution was degassed for 20 min with argon. Sodium carbonate (0.11 g, 0.8 mmol) in degassed H₂O (2 mL) was added, followed by 4-chlorobenzenboronic acid (0.17 g, 1.1 mmol). The resulting solution was heated to 110°C for 14 hrs. The solvent was evaporated, the residue was dissolved in CH₂Cl₂ (15 mL), and the solution was treated with HSiMe₃ (3 eq) and TFA (10 eq). The solvent was evaporated and the residue was purified by prep HPLC and converted to HCl salt as described for Example 48 to provide Example 60 (40 mg, 40%) as a gray solid.
MS (M+H)⁺ 493

¹H-NMR (CD₃OD, 300MHz) δ 2.95 (br m, 1H), 3.30 (m, 1H), 4.00 (br s, 1H), 4.20 (br s, 1H), 4.40 (br d, 1H), 4.60 (m, 1H), 4.65 (m, 1H), 5.05 (s, 1H), 6.05 (d, 1H), 7.00 (d, 1H), 7.15-8.10 (m, 13H), 8.85 (s, 1H), 8.95 (s, 1H).

5

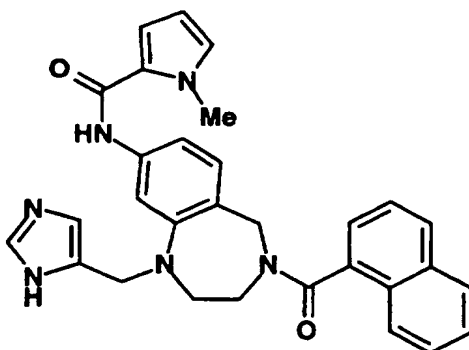
Example 61

10 **7-(3-Aminophenyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, trihydrochloride.**

Compound 61 was prepared as a gray solid in 45% yield from Compound A of Example 37 and 3-aminobenzeneboronic acid (0.17 g, 1.1 mmol) as described for Example 60.

15 MS (M+H)⁺ 474

¹H-NMR (CD₃OD, 300MHz) δ 2.95 (br m, 1H), 3.30 (m, 1H), 4.00 (br s, 1H), 4.20 (br s, 1H), 4.40 (br d, 1H), 4.60 (m, 1H), 4.65 (m, 1H), 5.05 (s, 1H), 6.05 (d, 1H), 7.00 (d, 1H), 7.15-8.10 (m, 13H), 8.85 (s, 1H), 8.95 (s, 1H).

Exempl 62

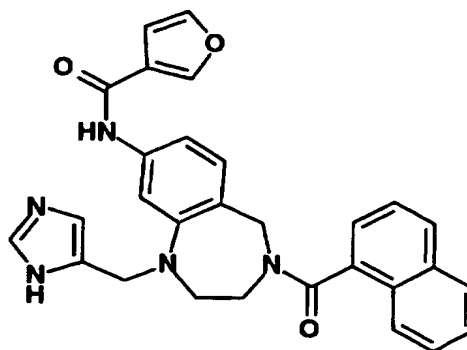
- 5 **1-Methyl-N-[2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepin-8-yl]-1H-pyrrole-2-carboxamide, trihydrochloride.**

Example 26 (0.050 g, 0.12 mmol) was added to a solution of EDC
 10 (0.071, 0.37 mmol), HOAt (0.051 g, 0.37 mmol) and 1-methyl-2-pyrrolecarboxylic acid (0.046 g, 0.37 mmol) in DMF (1 mL). After stirring for 16 hr, the mixture was diluted with CHCl₃ (10 mL) and NaHCO₃ (3 mL) and stirred for 30 min. The layers were separated and the aqueous layer was reextracted with CHCl₃ (2 x 20 mL). The combined organic layers were
 15 dried over MgSO₄, filtered and concentrated. The residue was purified on a silica gel column eluting with CHCl₃ followed by CHCl₃/MeOH (19/1). The product was treated with HCl/ether to afford a yellow solid which was triturated with ether few times and dried under vacuum to afford Example 62 (0.007 g, 11 %) as a light brown solid.

20 MS (M+H)⁺ 505

¹H NMR (270 MHz, CD₃OD): d 8.88 (d, 1H, J = 21Hz), 8.07-7.9 (m, 2.5H), 7.72-7.4 (m, 5H), 7.3 (d, 0.5H, J = 8Hz), 7.23 (d, 0.5H, J = 8Hz), 7.16 (d, 0.5H, J = 8 Hz), 7.0 (m, 0.5H), 6.95-6.85 (m, 1H), 6.7 (d, 0.5H, J = 8Hz), 6.15-6.1 (m, 1H), 5.92 (d, 0.5H, J = 8Hz), 5-4.9 (m, 2H), 4.65-4.15 (m, 4H), 3.98-3.9 (d, 3H, J = 10), 3.43-3.3 (m, 2.5H), 3.05-2.87 (m, 1H).

25

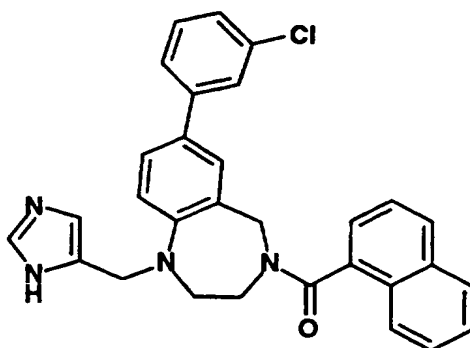
Exempl 63

- 5 **N-[2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepin-8-yl]-3-furancarboxamide, dihydrochloride.**

10 Example 63 was prepared as a yellow solid from Example 26 and 3-furoic acid as described for Example 62.

MS (M+H)⁺ 492

15 ¹H NMR (270 MHz, CD₃OD): d 8.88 (d, 1H, J = 20 Hz), 8.25 (d, 1H, J = 16 Hz), 8.13-7.38 (m, 9H) 7.38 (d, 0.5H, J = 6 Hz), 7.25 (0.5 H, J = 6Hz) 7.19 (d, 0.5H, J = 8Hz), 6.95 (d, 0.5H, J = 17 Hz), 6.72-6.68 (m, 1H), 5.93 (d, 0.5H, J = 8Hz), 5.0-4.9 (m, 2H), 4.66-3.91(m, 3.5H), 3.4-3.3 (m, 2H), 3.05-2.89 (m, 1H).

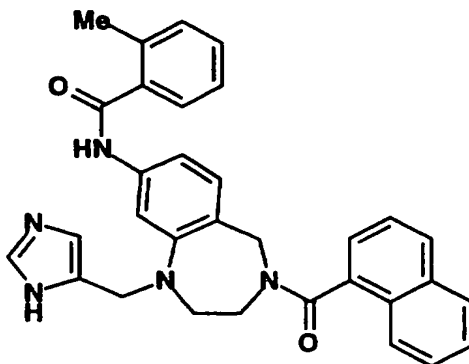
Example 64

- 5 **7-(3-Chlorophenyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, dihydrochloride.**

Compound 64 was prepared as a gray solid in 55% yield from
 10 Compound A of Example 37 and 3-chlorobenzenboronic acid (0.17 g, 1.1 mmol) as described for Example 60.

MS (M+H)⁺ 493

¹H-NMR (CD₃OD, 300MHz) δ 2.95 (br m, 1H), 3.30 (m, 1H), 4.00 (br s, 1H),
 4.20 (br s, 1H), 4.40 (br d, 1H), 4.60 (m, 1H), 4.65 (m, 1H), 5.05 (s, 1H), 6.05
 15 (d, 1H), 7.00 (d, 1H), 7.15-8.10 (m, 13H), 8.85 (s, 1H), 8.95 (s, 1H).

Example 65

20

2-Methyl-N-[2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepin-8-yl]benzamide, dihydrochloride.

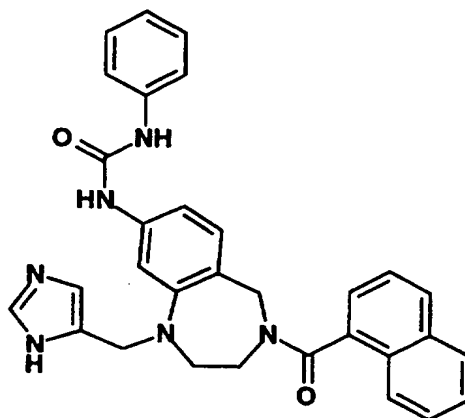
Example 65 was prepared as a light yellow solid in 23% yield from o-toluoyl chloride and Example 26 as described for Example 56.

MS (M+H)⁺ 516

- 5 ¹H NMR (270 MHz, CD₃OD): d 8.8 (d, 1H, J = 20 Hz), 8.05-7.2 (m, 13.5H), 7.1 (d, 0.5H, J = 6Hz), 6.7 (d, 0.5H, J = 8 Hz), 5.95 (d, 0.5H, J = 8 Hz), 5.1-4.9 (m, 2H), 4.7-3.9 (m, 3H), 3.45-3.3 (m, 2H), 3.8-2.9 (m, 1H), 2.5-2.4 (d, 3H, J = 15Hz).

10

Example 66



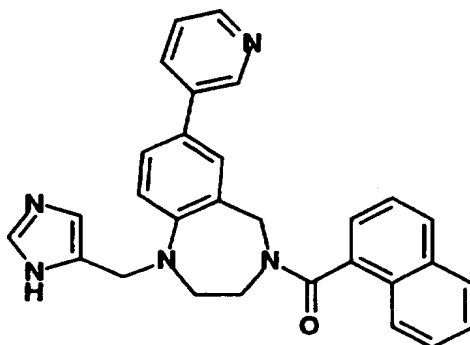
- 15 **N-Phenyl-N'-[2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepin-8-yl]urea, dihydrochloride.**

- 20 Phenyl isocyanate (0.016 mL, 0.15 mmol) was added to a solution of Example 26 (0.050 g, 0.12 mmol) and triethyl amine (0.020 mL, 0.15 mmol) in CH₂Cl₂ (1 mL). After stirring for 16 hr, the reaction was diluted with CHCl₃ (10 mL) and NaHCO₃ (3 mL) and stirred for 30 min. The layers were separated and the aqueous layer was reextracted with CHCl₃ (2 x 20 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated. The residue purified on a silica gel eluting with (19/1) CHCl₃/CH₃OH. The appropriate fractions were concentrated and the residue was treated with HCl/ether. The solid was triturated with ether several times and dried under vacuum to afford Example 66 (0.018 g, 25 %) as a light yellow solid.

25 MS (M+H)⁺ 517

¹H NMR (400 MHz, CD₃OD): d 8.83 (d, 1H, J = 19Hz), 8.07-7.89 (m, 2H), 7.68-7.2 (m, 11.5H), 7.07-6.98 (m, 1H) 6.85 (d, 0.5H, J = 6Hz), 6.4 (d, 0.5H, J = 8Hz), 5.89 (d, 0.5H, J = 8Hz), 5.1-4.9 (m, 1H), 4.69-3.9 (m, 4H), 3.45-3.3 (m, 2H), 3.05-2.88 (m, 1H).

5

Example 67

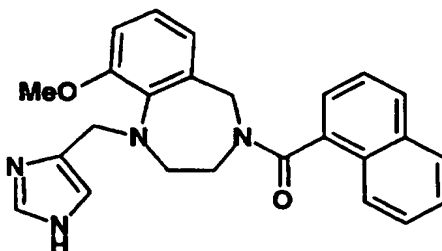
10 **2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-7-(3-pyridinyl)-1H-1,4-benzodiazepine, trihydrochloride.**

Example 67 was prepared as a yellow solid in 8% yield from
 15 Compound A of Example 37 and 3-(tributylstannyl)pyridine as described for Compound B of Example 37.

MS: (M+H)⁺ 460

Example 68

20

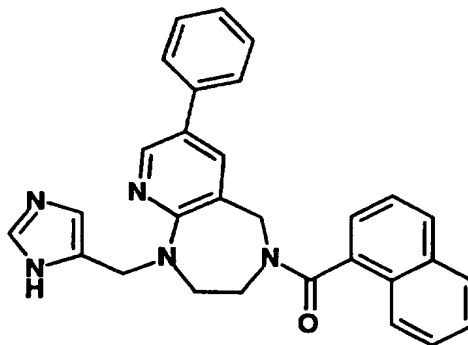


2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-9-methoxy-4-(1-naphthalenylcarbonyl)-1H-1,4-diazepine, dihydrochloride.

25

Example 68 was prepared as a light yellow solid from 8-methoxyisatoic anhydride and glycine ethyl ester hydrochloride as described in the following multistep sequence: Compound A of Example 1; Reduction was accomplished by refluxing a solution of the dione with 5 eq of borane-THF in THF for 20 hr; cooling to 0°C, acidifying with 3N HCl, heating at 100°C for 30 min, neutralizing with 5N NaOH followed by extraction with methylene chloride; Compound C of Example 2; Compound D of Example 1. MS (M+H)⁺ 413
IR: (KBr):- 2926, 2837, 1732, 1630, 1580, 1474, 1252, 1078, 804, 781 cm⁻¹.

Example 69



2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-7-phenyl-1H-pyrido[2,3-e]-1,4-diazepine, trihydrochloride.

A. 2,3,4,5-Tetrahydro-7-bromo-1H-pyrido[2,3-e]-1,4-diazepin-5-one

To a solution of Compound A of Example 23 (100 mg, 0.61 mmol) in acetic acid (10 mL) was added bromine (32 µL, 0.61 mmol). The mixture stirred for 30 minutes after which another equivalent of bromine (32 µL) was added to drive the reaction to completion. After an additional 30 minutes, the reaction was diluted with 30 mL H₂O and neutralized to pH 7 with 5 N NaOH. The mixture was extracted with Et₂O (50 mL) then with CH₂Cl₂ (2 x 100 mL). The organic layers were combined, washed with brine and dried over Na₂SO₄. Concentration gave Compound A as a solid (116 mg, 79%). MS (M+CH₃CN)⁺ 283.

B. 2,3,4,5-Tetrahydro-7-phenyl-1H-pyrido[2,3-]-1,4-diaz pin-5-on

A solution of Compound A (27 mg, 0.11 mmol), PhB(OH)₂ (34 mg, 0.28 mmol), and K₃PO₄ (59 mg, 0.28 mmol) in anhydrous DMF (0.6 mL) and anhydrous THF (0.6 mL) was degassed by bubbling with a stream of N₂ for 1 hour. To this solution was added recrystallized Pd(PPh₃)₄ and the solution was warmed to 65°C for 30 hours. The mixture was cooled to room temperature and diluted with CH₂Cl₂ (6 mL). This was extracted with 10% LiCl and the aqueous layer back-extracted once with CH₂Cl₂ (6 mL). The organic layers were combined and washed with 1 N HCl. The organic layer was discarded, and the aqueous layer was basified with 5 N NaOH and extracted with CH₂Cl₂ (3 x 10 mL). These organic layers were washed once more with 10% LiCl, dried over Na₂SO₄ and concentrated to give Compound B as a white solid (18 mg, 70%). MS (M+H+CH₃CN)⁺ 281.

C. 2,3,4,5-Tetrahydro-7-phenyl-1H-pyrido[2,3-e]-1,4-diazepine

Compound C was prepared as described for Compound B of Example 23, with refluxing for 60 hours. The crude material was chromatographed (flash silica, 230-400 mesh, 5-10% MeOH/CHCl₃) to give Compound C as a white solid (34%). MS (M+H+CH₃CN)⁺ 267.

D. 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-7-phenyl-1H-pyrido[2,3-e]-1,4-diazepine, trihydrochloride.

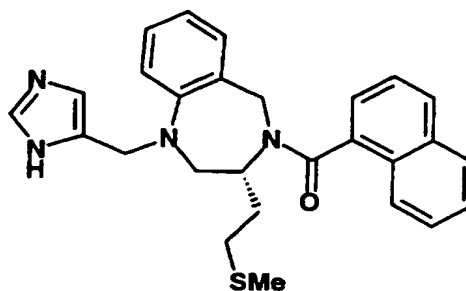
Example 69 was prepared as a fluffy white solid in 36% overall yield from Compound C as described for Compound C of Example 23 and Compound D of Example 23, with a total of 6 aliquots of aldehyde and hydride necessary to drive the reaction to completion.

MS (M+H)⁺ 460

Analysis calculated for C₂₉H₂₅N₅O • 3 HCl.

Calc'd: C, 61.22; H, 4.96; N, 12.31.

Found: C, 61.50 H, 5.21; N, 12.29.

Example 70

- 5 **(R)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-[2-(methylthio)ethyl]-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, hydrochloride.**

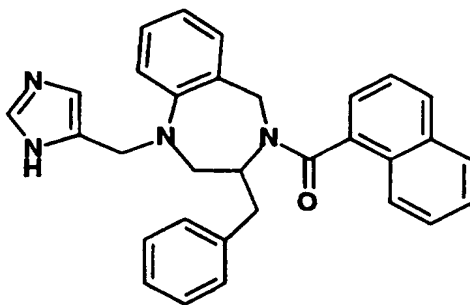
10 Example 70 was prepared as a yellow solid from isatoic anhydride and L-methionine-O methyl ester hydrochloride as described in the following sequence: Compound A of Example 1, with refluxing for 18 hours, evaporation of solvent and partitioning between 1N hydrochloric acid and dichloromethane; Example 17, except that the free base was carried on; Compound C of Example 2, with flash chromatography on silica eluting with ethyl acetate:hexane (1:2); Compound D of Example 1. mp 145-150°C.
15 MS (M+H)⁺ 456

Analysis calculated for C₂₇H₂₈N₄OS • 1.6 H₂O • 1.3 HCl.

Calc'd: C, 60.86; H, 6.15; N, 10.51; S, 8.65; Cl, 6.02.

Found: C, 60.96; H, 5.67; N, 10.14; S, 8.39; Cl, 5.68.

20

Example 71

- 5 **2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, hydrochloride.**

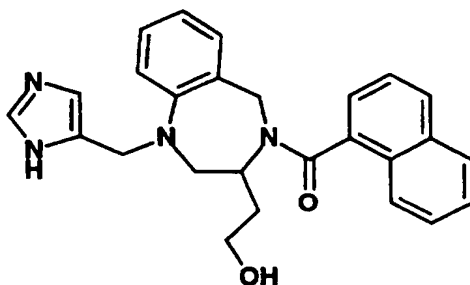
Example 71 was prepared as a yellow solid from isatoic anhydride
 10 and D,L-phenylalanine-O methyl ester hydrochloride as described for Example 70. mp 78-80°C.

MS (M+H)⁺ 473

Analysis calculated for C₃₁H₂₈N₄O • 1.6 H₂O • 1.8 HCl.

Calc'd: C, 65.66; H, 5.87; N, 9.88; Cl, 11.25.

15 Found: C, 65.85; H, 5.68; N, 9.64; Cl, 11.55.

Example 72

20

2,3,4,5-Tetrahydro-3-(2-hydroxyethyl)-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, trifluoroacetate.

25 Example 72 was prepared as a white solid from isatoic anhydride and D,L-aspartate-O-dimethyl ester hydrochloride as described for Example

70, except that 5 equivalents of lithium aluminum hydride were used in the reduction step, and the final product was purified by preparative HPLC (gradient of aqueous methanol with 0.1% TFA). mp 155-160°C.

MS (M+H)⁺ 427

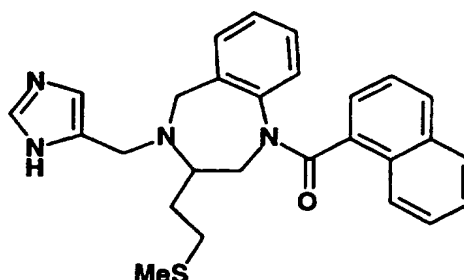
5 Analysis calculated for C₂₆H₂₆N₄O₂ • 1.0 H₂O • 1.3 TFA.

Calc'd: C, 57.95; H, 4.98; N, 9.45; Cl, 11.25.

Found: C, 58.09; H, 4.71; N, 9.32; Cl, 11.55.

Example 73

10



15 **2,3,4,5-Tetrahydro-4-(1H-imidazol-4-ylmethyl)-3-[2-(methylthio)ethyl]-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, trifluoroacetate.**

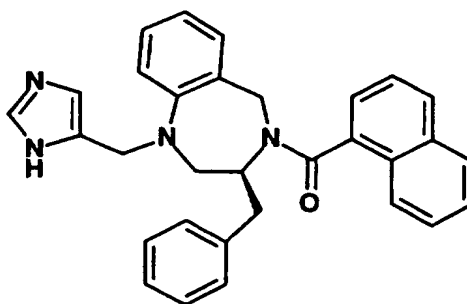
Example 73 was prepared from 2,3,4,5-tetrahydro-3-[2-(methylthio)ethyl]-1H-1,4-benzodiazepine (prepared from D,L-methionine-O methyl ester hydrochloride as described in Example 70) by the following
20 procedure: Compound A of Example 4; Compound C of Example 2, carried on without purification; Compound C of Example 4; Compound D of Example 1, with purification by preparative HPLC (gradient of aqueous methanol with 0.1% TFA). mp 130-135°C.

MS (M+H)⁺ 456

25 Analysis calculated for C₂₇H₂₈N₄OS • 1.5 H₂O • 1.3 TFA.

Calc'd: C, 56.27; H, 5.15; N, 8.87; S, 5.07; F, 11.73.

Found: C, 56.24; H, 4.84; N, 8.74; S, 5.10; F, 12.05.

Example 74

- 5 **(S)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate.**

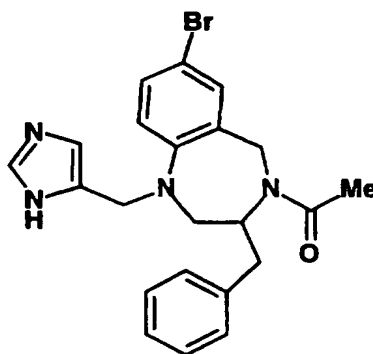
Example 74 was prepared as a white solid from isatoic anhydride
10 and L-phenylalanine-O methyl ester hydrochloride as described for Example 70, with final purification by preparative HPLC (gradient of aqueous methanol with 0.1% TFA). mp 152-154°C.

MS (M+H)⁺ 473

Analysis calculated for C₃₁H₂₈N₄O • 1.0 H₂O • 1.2 TFA.

15 Calc'd: C, 63.94; H, 5.01 N, 8.93; Cl, 10.90.

Found: C, 64.12; H, 4.87; N, 8.73; Cl, 11.01.

Example 75

20

4-Acetyl-7-bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, hydrochloride.

A. 7-Bromo-2,3,4,5-Tetrahydro-3-(phenylmethyl)-1H-1,4-benzodiazepine

A mixture of bromoisatoic anhydride (2.93 g, 12.1 mmol), D,L-phenylalanine-O methyl ester hydrochloride salt (2.62 g, 12.1 mmol),
5 dimethylaminopyridine (100 mg, catalytic) and pyridine (50 ml) was refluxed (bath temperature ~140 °C) under argon for 48 hours. The solution was concentrated in vacuo to a semi-solid and the residue was suspended in 1N HCl (200 mL) and dichloromethane (200 mL). The resultant precipitate
10 was filtered and washed with dichloromethane (50 mL) and dried in vacuo at 50°C for 18 hrs to provide Compound A (1.1 g, 26 %) as a gray solid.

B. 7-Bromo-2,3,4,5-Tetrahydro-3-(phenylmethyl)-1H-1,4-benzodiazepine

To a solution of Compound A (500 mg, 1.45 mmol) in ethylene glycol dimethyl ether (anhydrous, 50 mL) under argon at 0° C was slowly
15 added a solution of BH₃:THF (20 mL, 1M solution in THF). The solution was allowed to warm to room temperature, heated to reflux for 18 hours, cooled to 0°C, quenched with methanol (5 mL), and concentrated in vacuo to an oil. The oil was treated with 6 M HCl (100 mL), on a steam bath for 2 hours,
20 during which time partial dissolution occurred. The mixture was cooled to 0°C and adjusted to pH 10 with solid NaOH. The resultant mixture was partitioned in ethyl acetate (200 mL) and extracted with ethyl acetate (2 x 100 mL), dried (Na₂SO₄) and concentrated in vacuo to provide Compound B as a brown solid (300 mg, 0.94 mm, 65 %)

C. 4-Acetyl-7-bromo-2,3,4,5-tetrahydro-3-(phenylmethyl)-1H-1,4-benzodiazepine

A mixture of Compound B (200 mg, 0.63 mmol), dichloromethane (5 mL), and aqueous sodium hydroxide (1 ml, 1N) was combined and cooled
30 to 0°C. Acetyl chloride (66 mL, 0.94 mmol) was added to the mixture, and after stirring for 2 hour at 0°C aqueous sodium hydroxide (20 ml, 1N) and dichloromethane (50 mL) were added, followed by extraction with dichloromethane (50 mL). The organic portions were combined, dried (Na₂SO₄), and concentrated to a crude oil (230 mg, 100 %).

D. 4-Ac tyl-7-br mo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine

Example 75 was prepared as a white solid from Compound C as described for Compound D of Example 1, with purification of the final product by preparative HPLC (gradient of aqueous methanol with 0.1% TFA). mp 112°C.

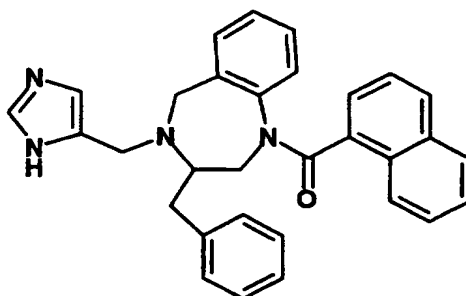
MS (M+H)⁺ 440

Analysis calculated for C₂₂H₂₃N₄OBr • 0.5 H₂O • 1.3 TFA.

Calc'd: C, 49.53; H, 4.27 N, 9.39; F, 12.42.

Found: C, 49.44; H, 4.07; N, 9.34; F, 12.32.

Example 76



2,3,4,5-Tetrahydro-4-(1H-imidazol-4-ylmethyl)-1-(1-naphthalenyl-carbonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, 1.5 hydrochloride.

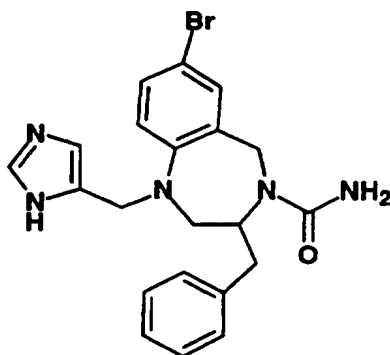
Example 76 was prepared as a white solid from 2,3,4,5-tetrahydro-3-(phenylmethyl)-1H-1,4-benzodiazepine (prepared as described in Example 71) by the following procedure: Compound A of Example 4; Compound C of Example 2, with catalytic pyridine and purification on silica eluting with hexane: ethyl acetate (4:1); Compound C of Example 4; Compound D of Example 1, with purification by preparative HPLC (gradient of aqueous methanol with 0.1% TFA). mp 117-120°C.

MS (M+H)⁺ 473

Analysis calculated for C₃₁H₂₈N₄OBr • 0.8 H₂O • 1.52 TFA.

Calc'd: C, 61.92; H, 4.75 N, 8.48; F, 13.12.

Found: C, 62.31; H, 4.40; N, 8.09; F, 12.76.

Example 77

5 **7-Bromo-1,2,3,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4H-1,4-benzodiazepine-4-carboxamide, trifluoroacetate.**

10 **A. 7-Bromo-1,2,3,5-tetrahydro-3-(phenylmethyl)-4H-1,4-benzodiazepine-4-carboxamide**

A mixture of Compound B of Example 75 (200 mg, 0.63 mmol,), THF (20 mL), and trimethylsilylisocyanate (0.13 mL, 0.95 mmol) was stirred under argon at room temperature for 18 hours. Water was added to the solution (5 mL), followed by aqueous hydrochloric acid (20 ml, 1 N). The mixture was extracted with ethyl acetate (2 x 100 mL), the organic extracts were combined, dried (MgSO₄), and concentrated in vacuo to provide Compound A as a yellow solid (200 mg, 88 %)

20 **B. 7-Bromo-1,2,3,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4H-1,4-benzodiazepine-4-carboxamide, trifluoroacetate.**

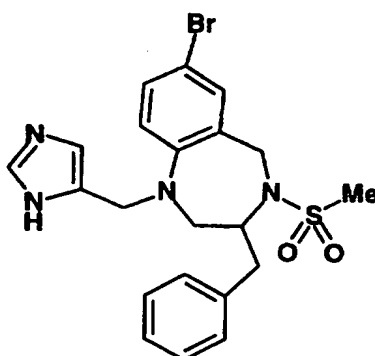
Example 77 was prepared as a white solid from Compound A as described for Compound D of Example 1, with purification by preparative HPLC (gradient of aqueous methanol with 0.1% TFA). mp 162-165°C.

25 MS (M+H)⁺ 440

Analysis calculated for C₂₁H₂₂N₅OBr • 0.3 H₂O • 1.2 TFA.

Calc'd: C, 48.24; H, 4.12 N, 12.02; Br, 13.72; F, 11.74.

Found: C, 48.23; H, 3.91; N, 11.95; Br, 13.63; F, 11.39.

Example 78

5 **7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methanesulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, hydrochloride**

10 **A. 7-Bromo-2,3,4,5-tetrahydro-4-(methanesulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine**

A mixture of Compound B of Example 75 (1.0 g, 3.15 mmol,), THF (20 mL), DIEA (0.6 mL, 6.3 mmol) and methanesulfonyl chloride (0.5 mL, 6.3 mmol) was stirred under argon at room temperature for 2 hours. The mixture was partitioned in aqueous hydrochloric acid (100 ml, 1 N), and ethyl acetate (100 mL). The aqueous phase was extracted with ethyl acetate (2 x 100 mL) and the combined organic layers were combined, dried (MgSO₄) and concentrated under vacuum to provide an oil. The oil was flash chromatographed (50 g silica eluted with hexane:ethyl acetate (3:1) to provide Compound A as a clear oil (330 mg, 27 %).

20

B. 7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methanesulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, hydrochloride

To a stirred solution of Compound A (330 mg, 0.84 mmol), formyl imidazole (120 mg, 1.26 mmol), dichloroethane (10 mL) and acetic acid (2 mL) at room temperature was added sodium triacetoxyborohydride (267 mg, 1.26 mmole). The solution was stirred for 1 hour, diluted with ethyl acetate (20 mL) and ammonium hydroxide (2 ml, conc), and stirred for an additional 18 hours. The mixture was extracted with ethyl acetate (2 x 25 mL), and the combined organic extracts were washed with aqueous sodium bicarbonate

30

(25 ml, saturated solution) and ammonium chloride (25 mL, sat aqueous solution), dried (Na_2SO_4), and concentrated in vacuo to a semi-solid. The crude was purified by preparative HPLC (gradient of aqueous methanol with 0.1% TFA) and lyophilized to provide the TFA salt of Example 78 as a white solid (330 mg, 83 %), mp 118-120 °C. This material was dissolved in methanol (3 mL) and 1M HCl (3 mL) was added. The solution was evaporated and the residue triturated with methylene chloride to provide Example 78 as a white solid, mp 178-180 °C.

MS ($\text{M}+\text{H}$)⁺ 476

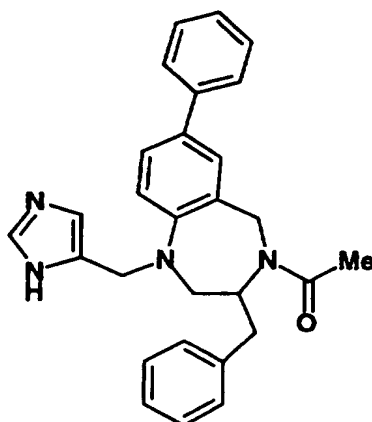
Analysis calculated for $\text{C}_{21}\text{H}_{23}\text{N}_4\text{O}_2\text{SBr} \cdot 0.25 \text{ H}_2\text{O} \cdot 1.2 \text{ HCl}$.

Calc'd: C, 48.17; H, 4.75; N, 10.70; S, 6.12; Cl, 8.12; Br, 15.26.

Found: C, 48.53; H, 4.60; N, 10.25; S, 6.95; Cl, 8.27; Br, 14.93.

15

Example 79



4-Acetyl-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-3-(phenylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate.

A. 4-Acetyl-2,3,4,5-tetrahydro-7-phenyl-3-(phenylmethyl)-1H-1,4-benzodiazepine

To a solution of Compound C of Example 75 (500 mg, 1.39 mmol) in toluene (20 mL), and NaHCO_3 (5 mL, sat solution) under argon was added a solution of phenylboronic acid (340 mg, 2.8 mmol, in 2 mL ethanol). Tetrakis(triphenylphosphine) palladium(0) (42 mg, 0.07 mmol) was added to the mixture and it was brought to reflux under argon for three hours. The mixture was poured into brine, extracted with ethyl acetate (2 x 100 mL), the

organics combined and dried (MgSO₄), and concentrated in vacuo to provide a crude red oil, which was purified by flash chromatography (50 g silica eluted with hexane:ethyl acetate 1:1 to provide Compound A as a white solid (290 mg, 59 %).

5

B. 4-Acetyl-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-3-(phenylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate.

Example 79 was prepared as a white solid in 79% yield from Compound A as described for Compound D of Example 1, with purification by preparative HPLC (gradient of aqueous methanol with 0.1% TFA). mp 120-123°C.

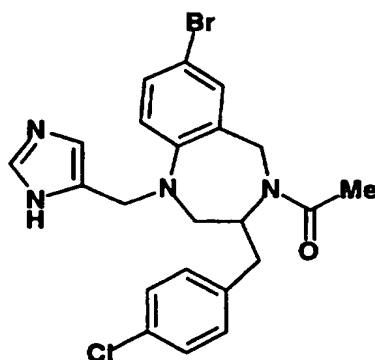
MS (M+H)⁺ 437

Analysis calculated for C₂₈H₂₈N₄O • 1.3 H₂O • 1.05 TFA.

15 Calc'd: C, 62.36; H, 5.50 N, 9.66; F, 10.32.

Found: C, 62.42; H, 5.17; N, 9.61; F, 10.24.

Example 80



20

4-Acetyl-7-bromo-3-[(4-chlorophenyl)methyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.

25

A. D,L-N-(2-Amino-5-bromobenzoyl)-4-chlorophenylalanine

D,L-4-chlorophenylalanine (prepared from N-Boc-D,L-4-chlorophenylalanine and 4N HCl in dioxane with dimethyl sulfide) and 6-bromoisatoic anhydride (1.0 g, 4.15 mmol) were combined in pyridine (50 mL) and the mixture was refluxed for 4 h. The mixture was cooled,

30

concentrated and the residue was partitioned between water (200 mL) and ethyl acetate (200mL). The organic layer was washed with water (3X100mL), brine (50 mL), dried (MgSO₄) and concentrated to yield Compound A as a yellowish glass (450 mg, 27 %), MS (M+H)⁺ 398.

5

B. 7-bromo-3-[(4-chlorophenyl)methyl]-2,3,4,5-tetrahydro-1H-1,4-benzodiazepin-2,5-dione

Compound A (450 mg, 1.13 mmol), EDC (737 mg, 3.85 mmol), and HOBt (519 mg, 3.85 mmol) were dissolved in DMF (10 mL) and DIEA (0.52 mL, 2.96 mmol) was added at once. The mixture was stirred for 16 h, poured into water (100 mL) and the product was extracted with ethyl acetate (2X50 mL). The combined ethyl acetate layers were washed with water (3X100 mL), brine (100 mL), dried (MgSO₄) and concentrated to yield compound B as a brown glass (200 mg, 46 %), MS (M+H)⁺ 380.

15

C. 7-bromo-3-[(4-chlorophenyl)methyl]-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine

Compound B (200 mg, 0.53 mmol) was dissolved in THF (10 mL) and borane (1M in THF, 4 mL, 4 mmol) was added. The solution was refluxed for 3 h and cooled to room temperature. Methanol (5 mL) was added and the solution was concentrated. 5N HCl (10 mL) was added to the concentrate and the mixture was refluxed for 4 h. The mixture was cooled to room temperature, neutralized to pH 6 with 50% NaOH and extracted with methylene chloride (3X50 mL). The organic layers were combined, washed with brine (30 mL), dried (MgSO₄) and concentrated to yield compound C as a slightly yellow glass (60 mg, 32 %), MS (M+H)⁺ 352.

25

D. 4-Acetyl-7-bromo-3-[(4-chlorophenyl)methyl]-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine

Compound D (60 mg, 0.17 mmol) was dissolved in THF (5 mL) and DIEA (30 μ L, 0.17 mmol) was added followed by acetyl chloride (12 μ L, 0.17 mmol). The solution was stirred for 30 min, concentrated, redissolved in ethyl acetate (50 mL) and washed with water (3X20 mL). The organic layer was dried (MgSO₄) and concentrated to yield Compound D as a light brown glass.

35

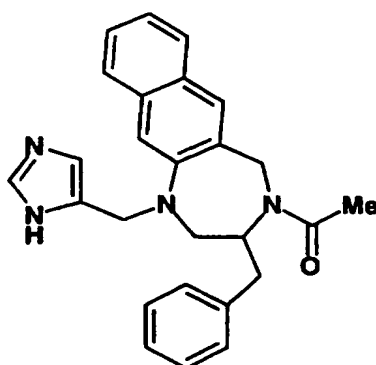
E. 4-Acetyl-7-bromo-3-[(4-chlorophenyl)methyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-1H-1,4-benzodiazepine, dihydrochlorid

Example E was prepared from Compound D as a white solid in 13% yield as described for Compound D of Example 1, with purification by preparative HPLC (YMC S-5 ODS-A column, 30 X 250 mm; solvent A, 0.1% TFA in 90% water, 10 % methanol; solvent B, 0.1% TFA in 10% water, 90% methanol: 20-100% B in 60 min, flow rate 25 mL/min) and conversion to the HCl salt by adding 1N HCl to methanol solution of the TFA salt and lyophilizing.

MS (M+H)⁺ 475

¹H-NMR (CD₃OD, 400 MHz) δ 8.85 (1H, s), 7.49-7.15 (7H, m), 6.81 (1H, m), 4.60 (2H, m), 4.49-4.35 (2H, m), 3.63 (1H, m), 2.84-2.63 (2H, m), 2.07 (2H, m), 1.94 (3H, s).

Example 81



4-Acetyl-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-naphtho[2,3-e]-1,4-diazepine, monohydrochloride.

A. 2,3,4,5-Tetrahydro-3-(phenylmethyl)-1H-naphtho[2,3-e]-1,4-diazepin-2,5-dione

A solution of the 2,3-naphthyl analog of isatoic anhydride (prepared from 3-amino-2-naphthoic acid, 2.3 eq of triphosgene and triethyl amine in acetonitrile), D,L-phenylalanine (0.77g, 4.7 mmol) and pyridine hydrochloride (540 mg, 4.7 mmol) in pyridine (60 mL) was refluxed for 20 h under nitrogen followed by concentration to an oil. Water (100 mL) was

added and the solution was triturated to give a brown solid. This material was filtered and dried under high vacuum to give 1.3g (87%) of Compound A as a brown solid. MS (M+H)⁺ 317.

5 **B. 4-Acetyl-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-naphtho[2,3-e]-1,4-diazepine, monohydrochloride.**

Example 81 was prepared as an offwhite solid from Compound A by the following procedure: Compound C of Example 80; Compound D of
10 Example 80, with stirring for 1 hour and with purification by flash chromatography on silica with ethyl acetate:hexanes (1:5-1:1); Compound E of Example 80.

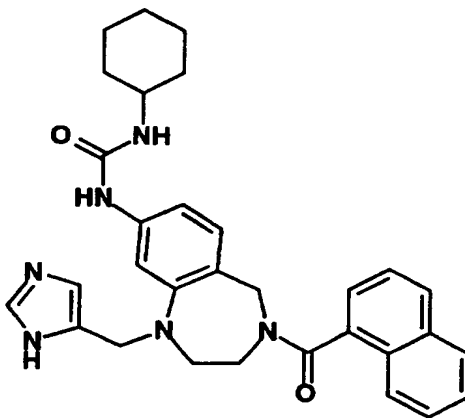
MS (M+H)⁺ 411

Analysis calculated for C₂₆H₂₆N₄O • 1.19 H₂O • 1.5 HCl.

15 Calc'd: C, 64.44; H, 6.17 N, 11.02; Cl, 10.71.

Found: C, 64.04; H, 6.38; N, 11.40; Cl, 10.90.

Example 82



20 **N-Cyclohexyl-N'-[2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepin-8-yl]urea, dihydrochloride.**

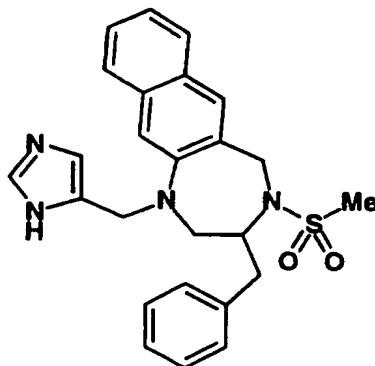
25

Example 82 was prepared from cyclohexylisocyanate as described for Example 66, with column chromatography performed with CHCl₃/CH₃OH (19/1 then 9/1).

MS (M+H)⁺ 523

¹H NMR (270 MHz, CD₃OD): d 8.83 (d, 1H, J = 19 Hz), 8.0-7.89 (m, 2.5H)
7.63-7.3 (m, 6.5H), 7.23 (d, 0.5H, J = 7Hz), 6.8 (d, 0.5H, J = 8Hz), 6.31 (d,
0.5H, J = 7 Hz), 5.83 (d, 0.5H, J = 8Hz), 4.8 (s, 1H), 4.6-3.8 (m, 4H), 3.6-3.5
(m, 1H), 3.45-3.3 (m, 2H), 3.0-2.8 (m, 1H), 1.9-1.58 (m, 5H), 1.48-1.13 (m,
5H).

Example 83

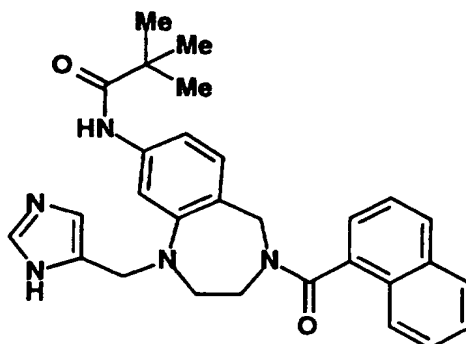


2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(phenylmethyl)-1H-naphtho[2,3-e]-1,4-diazepine, monohydrochloride.

Example 83 was prepared as an offwhite solid from 2,3,4,5-tetrahydro-3-(phenylmethyl)-1H-naphtho[2,3-e]-1,4-diazepine (prepared as described in Example 81) as described in Example 78.

MS (M+H)⁺ 447

¹H-NMR (CDCl₃, 400 MHz) d 8.72 (1H, m), 7.7-7.1 (12H, m), 5.01 (1H, m),
4.43 (1H, s), 4.41 (1H, s), 3.62 (1H, m), 3.15 (1H, m), 2.95 (1H, m), 2.72 (1H, m), 2.3 (3H, s).

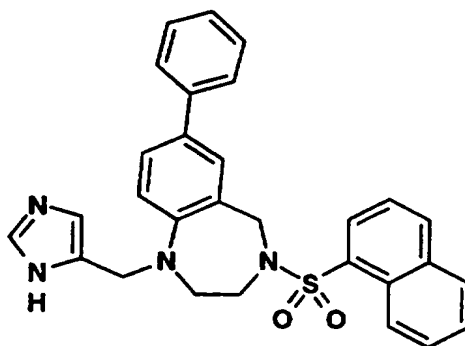
Example 84

- 5 **2,2-Dimethyl-N-[2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepin-8-yl]propanamide, dihydrochloride.**

Example 84 was prepared Example 26 and pivaloyl chloride as
 10 described for Example 27.

MS (M+H)⁺ 482

¹H NMR (270 MHz, CD₃OD): d 8.88 (d, 1H, J = 20 Hz), 8.05-7.89 (m, 2H),
 7.8-7.4 (m, 6.5H), 7.35 (d, 0.5H, J = 7 Hz), 7.22 (d, 0.5H, J = 7 Hz), 7.1 (d,
 0.5H, J = 8Hz), 6.6 (d, 0.5H, J = 8Hz), 5.9 (d, 0.5H, J = 8Hz), 4.6 (s, 1H), 4.5
 15 (m, 2H), 4.22-3.9 (m, 2H), 3.4-3.3 (m, 2H), 3.05-2.85 (q, 1H), 1.3 (d, 9H, J =
 16Hz).

Example 85

20

2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-phenyl)-1,4-benzodiazepine-7-sulfonamide, monohydrochloride .

A. 2,3,4,5-Tetrahydro-4-(1-naphthylsulfonyl)-7-phenyl-1H-1,4-benzodiazepine

To a solution of Compound B of Example 12 (500 mg, 2.2 mmol) in dichloromethane (20 mL) was added 1-naphthylsulfonyl chloride (500 mg, 2.2 mmol) and triethylamine (0.31 mL, 2.2 mmol). The solution was stirred for 1 h and concentrated. The residue was partitioned between saturated aqueous sodium bicarbonate (30 mL) and ethyl acetate (40 mL). The organic layer was washed with saturated aqueous sodium bicarbonate (2x30 mL), water (1x30 mL), 1M aqueous potassium hydrogen sulfate (3x30 mL), dried (Na₂SO₄) and concentrated to give 800 mg (88%) of Compound A as a white solid. MS (M+H)⁺ 415.2

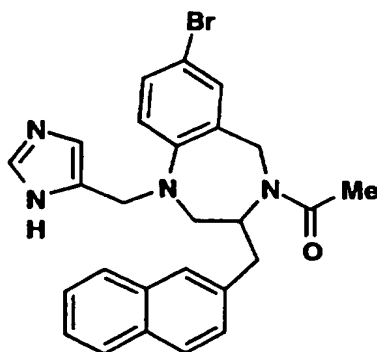
B. 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylsulfonyl)-7-phenyl-1H-1,4-benzodiazepine, monohydrochloride

Example 85 was prepared as an offwhite solid in 83% yield from Compound A as described for Compound D of Example 1.

MS (M+H)⁺ 415

¹H-NMR (CD₃OD, 270 MHz) δ 8.83 (1H, s), 8.5 (1H, m), 8.24 (1H, d, J=8Hz), 8.11 (1H, J=8 Hz), 7.94 (1H, m), 7.61-7.25 (9H, m), 7.02 (1H, d, J=8 Hz), 4.61 (2H, s), 4.41 (2H, s), 3.52 (2H, m), 3.09 (2H, m).

Example 86



4-Acetyl-7-bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(2-naphthalenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride .

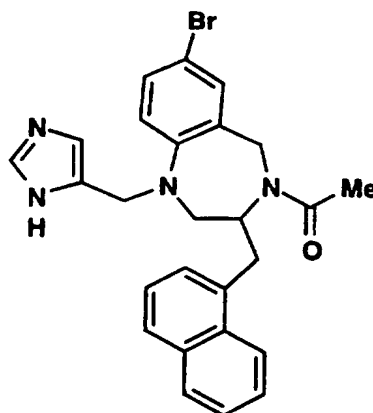
Example 86 was prepared as a white solid from D,L-2-naphthylalanine as described for Example 80.

MS (M+H)⁺ 475

- 5 ¹H-NMR (CD₃OD, 400 MHz) δ 8.81 (1H, s), 7.84 (4H, m), 7.70 (1H, m), 7.50-7.25 (5H, m), 6.87 (1H, m), 4.73-4.54 (3H, m), 4.43 (1H, m), 3.73 (1H, m), 3.23 (1H, m), 3.05 (1H, m), 2.93 (1H, m), 2.13 (1H, m), 2.05 (3H, s).

Example 87

10

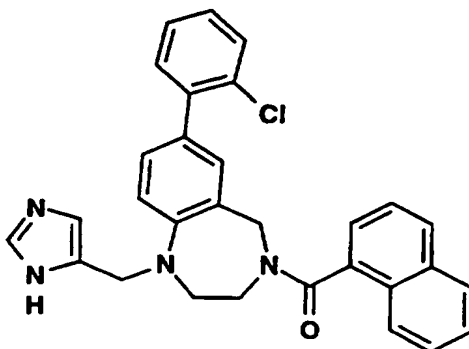


- 15 **4-Acetyl-7-bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(1-naphthalenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.**

Example 87 was prepared as a white solid from D,L-1-naphthylalanine as described for Example 80.

MS (M+H)⁺ 475

- 20 ¹H-NMR (CD₃OD, 400 MHz) δ 8.53 (1H, s), 7.87 (1H, m), 7.74 (1H, m), 7.55-7.23 (8H, m), 6.74 (1H, m), 4.57-4.43 (2H, m), 4.15 (1H, m), 3.90 (1H, m), 3.83 (1H, m), 3.48 (2H, m), 3.12 (1H, m), 3.00 (1H, m), 2.06 (2H, m), 2.01 (3H, s).

Exempl 88

5 **7-(2-Chlorophenyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, dihydrochloride.**

A. 2-Chlorobenzeneboronic acid

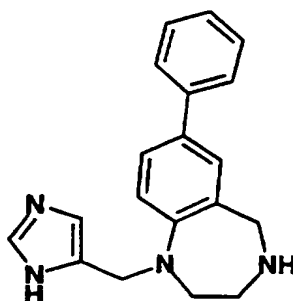
10 Borane-THF (100 mL, 100 mmol) was slowly added to a mixture of 2-bromochlorobenzene (5.4 mL, 46 mmol) and magnesium (ribbon, 1.12 g, 46 mmol). The flask was placed in a water bath and sonicated overnight. Water (30 mL) was slowly added to destroy excess borane. The aqueous solution was refluxed for 2 hrs. The solvent was evaporated and the residue
 15 was neutralized with aq HCl. The aqueous solution was extracted with ether (2x50 mL), dried (Na₂SO₄) and evaporated to afford Compound A (6.24 g, 86%).

B. 7-(2-Chlorophenyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, dihydrochloride

Example 88 was prepared as a gray solid in 55% yield from Compound A and Compound A of Example 37 as described for Example 60.

MS (M+H)⁺ 493

25 ¹H-NMR (CD₃OD, 300MHz) δ 2.95 (br m, 1H), 3.30 (m, 1H), 4.00 (br s, 1H), 4.20 (br s, 1H), 4.40 (br d, 1H), 4.60 (m, 1H), 4.65(m, 1H), 5.05 (s, 1H), 6.05 (d, 1H), 7.00 (d, 1H), 7.15-8.10(m, 13H), 8.85 (s, 1H), 8.95(s, 1H).

Example 89

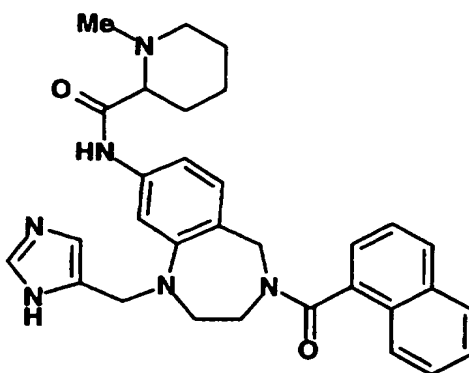
5 **2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, monohydrochloride.**

10 A solution of 2,3,4,5-tetrahydro-4-[(1,1-dimethylethoxy)-carbonyl]-7-phenyl-1H-1,4-benzodiazepine (prepared from Compound B of Example 12 as described for Compound A of Example 4, 0.20 g) and 4-formyl imidazole (0.52 g, 5.6 mmol) in CH₂Cl₂ (10 mL) and acetic acid (2 mL) was stirred for 40 min. Sodium triacetoxyborohydride (0.9 g, 6 mmol) was added and stirring was continued for 4 hrs. Sodium bicarbonate (sat., 5 mL) and ammonium hydroxide (conc, 5 mL) were added and the mixture was stirred for another 3 hrs. The aqueous layer was extracted with CH₂Cl₂ (3x50 mL). The combined organic layers were washed with 1N NaOH (2x10 mL) and conc. NH₄OH (10 mL), dried (Na₂SO₄) and evaporated. The residual solid was stirred in MeOH (5 mL) and aqueous HCl in dioxane (4 M, 10 mL) overnight. The solvent was evaporated and the residue was triturated with

15 CHCl₃ to give a solid (0.35 g) which was purified by preparative HPLC (methanol/water gradient with 0.1% TFA) and converted to the HCl salt by lyophilization from 1M HCl (5 mL) to provide Example 89 (0.12 g, 57%) as an off white solid.

MS (M+H)⁺ 305

25 ¹H-NMR (CD₃OD): 3.26 (m, 4H), 4.45 (s, 2H), 4.62 (s, 2H), 7.2-7.8 (m, 10H), 8.95 (s, 1H).

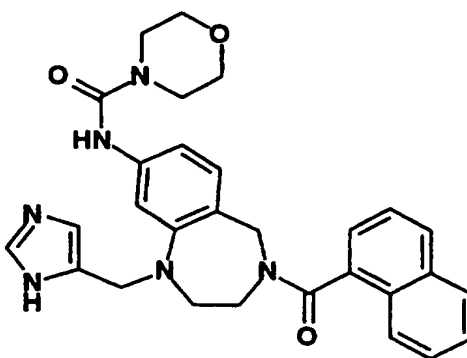
Exempl 90

- 5 **1-Methyl-N-[2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepin-8-yl]-2-piperidinecarboxamide, trihydrochloride.**

Example 90 was prepared as a light yellow solid from Example 26
 10 and N-methyl-pipecolic acid as described for Example 62.

MS (M+H)⁺ 523

¹H NMR (270 MHz, CD₃OD): δ 8.9 (d, 1H, J = 22 Hz), 8.08-7.88 (m, 2.5H),
 7.7-7.2 (m, 6H), 6.8 (d, 0.5H), 5.9 (m, 0.5H), 5.0 (m, 1.5H), 4.6 (s, 1H), 4.5 (m,
 2H), 4.3-4.1 (m, 1H), 4.05-3.9 (m, 1H), 3.6-2.7 (m, 8H), 2.3 (t, 1H), 2.05-1.56
 15 (m, 3H), 1.5 -0.8 (m, 3H).

Example 91

20

N-[2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepin-8-yl]-4-morpholin carb xamide, dihydrochloride.

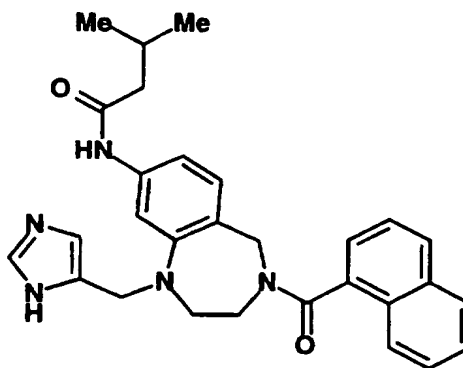
Example 91 was prepared as a light yellow solid from Example 26 and morpholine N-carbonyl chloride as described for Example 27.

MS (M+H)⁺ 511

- 5 ¹H NMR (270 MHz, CD₃OD): d 8.88 (q, 1H), 8.1-7.88 (m, 2.5H), 7.7-7.3 (m, 6.5H), 7.2 (t, 0.5H), 6.9 (d, 0.5H), 6.5 (d, 0.5H), 5.85 (d, 0.5H), 5.08-4.9 (m, 2H) 4.6-4.15 (m, 4H), 3.7-3.65 (m, 3H), 3.6-3.4 (m, 4H), 3.4-3.28 (m, 2H), 3.15-2.8 (m, 1H).

10

Example 92

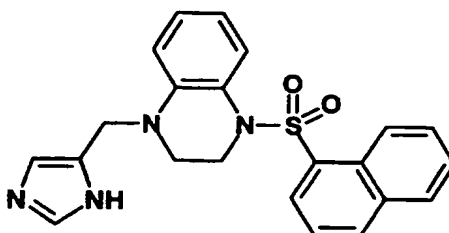


- 15 **N-[2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenyl-carbonyl)-1H-1,4-benzodiazepin-8-yl]-3-methylbutanamide, dihydrochloride.**

- 20 Example 92 was prepared as a light yellow solid in 67% yield from Example 26 and isobutyryl chloride as described for Example 27, except that the reaction mixture was concentrated after no starting material was observed, the residue was treated with MeOH and 1N NaOH for 30 min, and after workup, the product was treated with HCl/ether.

MS (M+H)⁺ 482

- 25 ¹H NMR (270 MHz, CD₃OD): d 8.88 (d, 1H, J = 21 Hz), 8.08-7.9 (m, 2.5H), 7.7-7.19 (m, 6.5H), 6.81 (d, 0.5H), 5.9 (d, 0.5H) 4.9 (m, 1H), 4.6-3.9 (m, 4H), 3.6-3.08 (m, 2H), 3.0-2.76 (m, 4H), 2.3 (m, 1H), 2.05-1.5 (m, 3H) 1.45-0.8 (m, 3H).

Example 93

5 **1,2,3,4-Tetrahydro-4-[(1H-imidazol-4-yl)methyl]-1-(naphthalen-1-ylsulfonyl)quinoxaline, dihydrochloride**

A. 1,2,3,4-Tetrahydro-1-(naphthalen-1-ylsulfonyl)quinoxaline

10 To a solution of Compound A of Example 3 (270 mg, 2 mmol) in dichloromethane (8 mL) at rt under argon was added triethylamine (0.42 mL, 3 mmol) and naphthalenesulfonyl chloride (500 mg, 2.2 mmol). After 18 hr, the mixture was washed successively with saturated NaHCO₃ and brine (10 mL each), dried (MgSO₄) and concentrated. Dichloromethane (1mL) was
15 added to the residual yellow solid and Compound A crystallized. The solution was purified by silica gel column chromatography eluting with 30% ethyl acetate in hexanes to afford additional Compound A, total yield 560 mg, 87%.

MS: (M+H)⁺ = 325⁺

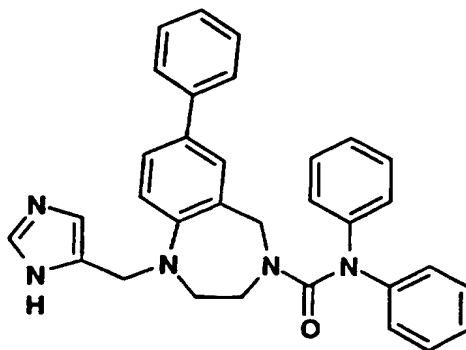
20

B. 1,2,3,4-Tetrahydro-4-[(1H-imidazol-4-yl)methyl]-1-(naphthalen-1-ylsulfonyl)quinoxaline, dihydrochloride

 Example 93 was prepared as a pale yellow solid from Compound A as described for Compound D of Example 1. Purification by flash silica gel
25 column chromatography eluting with 9:1 CHCl₃: MeOH afforded a solid which was converted to its HCl salt by treatment 1M HCl in ether (95 mg, 80%).

MS (M+H)⁺ 405

¹H NMR (free base) (CDCl₃) δ 8.22 (1H, d, J = 7.3 Hz), 8.15 (1H, d, J = 8
30 Hz), 8.02 (1H, d, J = 8 Hz), 7.87 (1H, d, J = 7.3 Hz), 7.49 (2H, t, J = 8 Hz), 7.39 (1H, s), 7.37 (1H, s), 7.31 (1H, t, J = 7.3 Hz), 7.26 (1H, s), 7.02 (1H, t, J = 7.3 Hz), 6.65 (1H, t, J = 7.3 Hz), 6.54 (1H, d, J = 8.0 Hz), 6.0 (1H, s), 4.0 (2H, s), 3.83 (2H, t, J = 5.3 Hz), 2.85 3.83 (2H, t, J = 5.3 Hz)

Example 94

5

1,2,3,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-N,N,7-triphenyl-4H-1,4-benzodiazepine-4-carboxamide, dihydrochloride.

Example 94 was prepared as a slightly pink powder from N,N-diphenylcarbonyl chloride as described for Example 35, mp >200°C.

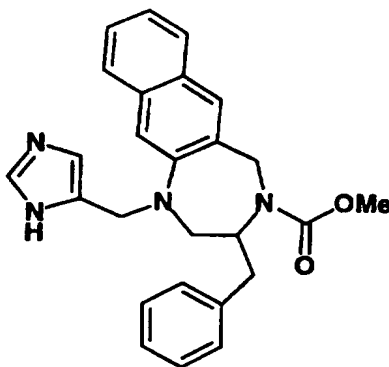
MS (M+H)⁺ 500

Analysis calculated for C₃₂H₂₉N₅O • 0.4 H₂O • 1.0 HCl.

Calc'd: C, 70.75; H, 5.71; N, 12.89; Cl, 6.53

Found: C, 70.89; H, 5.53; N, 12.77; Cl, 6.65.

15

Example 95

20

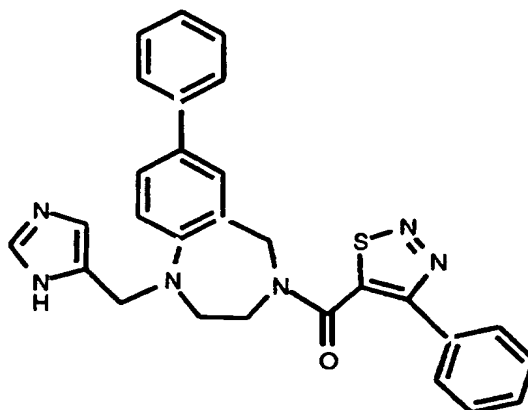
1,2,3,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4H-naphtho[2,3-b]-1,4-diazepine-4-carboxylic acid, methyl ester, monohydrochloride.

Example 95 was prepared as an off white solid from methyl chloroformate as described for Example 83.

MS (M+H)⁺ 427

5 ¹H-NMR(CD₃OD, 400 MHz) δ 8.72 (1H, m), 7.7-7.1 (12H, m), 5.01 (1H, m), 4.43 (1H, s), 4.41 (1H, s), 3.62 (1H, m), 3.15 (1H, m), 2.95 (1H, m), 2.72 (1H, m), 2.6 (3H, s).

Example 96



15 **2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-[(4-phenyl-1,2,3-thiadiazol-5-yl)carbonyl]-1H-1,4-benzodiazepine, trifluoroacetate.**

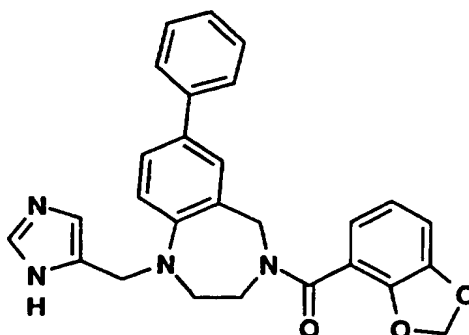
20 Example 96 was prepared as a white lyophilate in 50% yield from 4-phenyl-5-carboxy-1,2,3-thiadiazole as described for Example 34, with purification by preparative HPLC (gradient of aqueous methanol with 0.1% TFA).

MS (M+H)⁺ 493

Analysis calculated for C₂₈H₂₄N₆OS • 0.11 H₂O • 1.6 TFA.

Calc'd: C, 55.35; H, 3.84; N, 12.41

Found: C, 55.28; H, 3.71; N, 12.37.

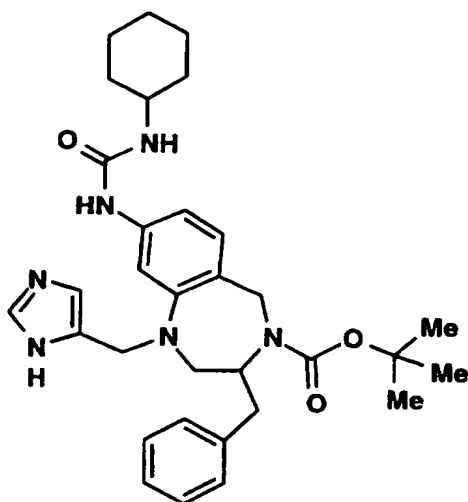
Example 97

- 5 **2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-[(4-phenyl-1,2,3-thiadiazol-5-yl)carbonyl]-1H-1,4-benzodiazepine, trifluoroacetate.**

10 Example 97 was prepared as a white lyophilate in 6% yield from 2,3-methylenedioxy-benzoic acid as described for Example 34, with purification by preparative HPLC (gradient of aqueous methanol with 0.1% TFA).

MS (M+H)⁺ 453

15 ¹HNMR(CD₃OD): 3.11 (m, 1 H), 3.61 (m, 1 H), 3.87 (br m, 2 H), 4.61-4.64 (m, 2 H), 5.81, 6.06 (s, 2 H), 5.96 (s, 2 H), 6.68-7.69 (m, 12 H), 8.42 (m, 1 H), 8.89 (m, 1 H).

Example 98

- 5 **8-[[[(Cyclohexylamino)carbonyl]amino]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine-4-carboxylic acid, 1,1-dimethylethyl ester.**

10 **A. 2,3,4,5-Tetrahydro-3-(phenylmethyl)-8-nitro-1H-1,4-benzodiazepin-2,5-dione**

Compound A was prepared from 7-nitroisatoic anhydride and phenylalanine as described for Compound A of Example 1, except that after refluxing for 1 day, the mixture was concentrated. Dimethyl acetamide was added and the mixture was heated at 150°C for 4 hr, concentrated and water
15 was added. The olive green solid obtained was filtered and air dried to obtain Compound A in 80 % yield). MS (M+H)⁺ 312

20 **B. 2,3,4,5-Tetrahydro-3-(phenylmethyl)-8-nitro-1H-1,4-benzodiazepine**

Borane in THF (1M, 86 mL) was added to Compound A (7.5 g, 24.01 mmol) and the mixture was refluxed for 2 days, cooled to rt, acidified with 3N HCl, and steam heated for 30 min. The solid was filtered and dried to afford Compound B (3.75 g, 95 %) as an olive green solid. MS (M+H)⁺ 254. The filtrate was made basic with 5N NaOH (pH 8-9) and extracted with
25 CHCl₃, dried over MgSO₄, filtered and concentrated to afford 2,3,4,5-tetrahydro-3-(phenylmethyl)-8-amino-1H-1,4-benzodiazepine (1.1 g, 21%).

C. 8-Nitro-2,3,4,5-tetrahydro-3-(phenylmethyl)-1H-1,4-benzodiazepine-4-carboxylic acid, 1,1-dimethylethyl ester

Boc anhydride (1.5 g, 7 mmol) was added to a solution of Compound B (2.0 g, 7 mmol) and triethylamine (0.71 g, 7 mmol) in THF (30 mL) under argon. After stirring for 6 hr, the mixture was extracted with CHCl₃ (3 x 70 mL). The combined extracts were washed with water (2 x 50 mL), and brine (1 x 50 mL), dried over MgSO₄, filtered and concentrated. The residue was triturated with hexane/CHCl₃ to afford Compound C as an olive green solid (0.89 g, 34 %). MS (M-H)⁻ 382

D. 8-Nitro-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine-4-carboxylic acid, 1,1-dimethylethyl ester

Compound D was prepared from Compound C as described for Compound D of Example 1, with stirring for 15 hours. MS (M+H)⁺ 464

E. 8-Amino-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine-4-carboxylic acid, 1,1-dimethylethyl ester

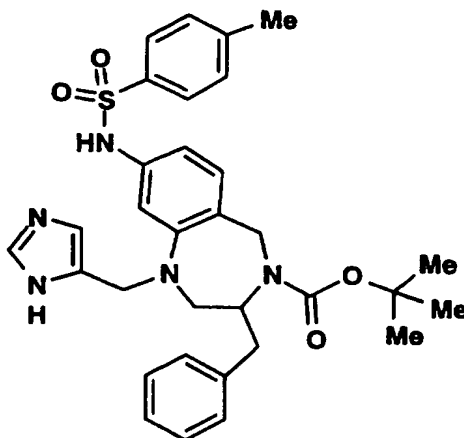
16 % aqueous TiCl₃ (2.66 g, in 15 mL H₂O, 17.2 mmol) was added to a solution of Compound D (1.0 g, 2.15 mmol) in AcOH/H₂O (16 mL, 1:1). After stirring for 15 min, the mixture was made basic with 5 N NaOH, stirred for 30 min and extracted with 10% isopropanol/CH₂Cl₂. The layers were separated, the aqueous layer was extracted with 10% isopropanol/CH₂Cl₂ and the combined organic layers were dried over MgSO₄, filtered and concentrated to afford Compound E (0.70g, 75 %). MS (M+H)⁺ 434.

F. 8-[[[(Cyclohexylamino)carbonyl]amino]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine-4-carboxylic acid, 1,1-dimethylethyl ester

Compound F was prepared from Compound E using the procedure described by Example 27, using cyclohexylisocyanate. The reaction mixture was concentrated and the residue was treated with 1 N NaOH and MeOH. After stirring for 30 min, the mixture was diluted with CHCl₃ and NaHCO₃. The layers were separated and the aqueous layer was reextracted twice with CHCl₃. The combined organic layers were washed with water, brine, dried

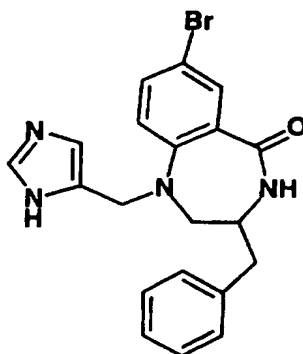
over MgSO_4 , filtered and concentrated to afford Example 98 as a light yellow solid. MS: $[\text{M}+\text{H}]^+ = 559^+$.
MS $(\text{M}+\text{H})^+ 559$

5

Example 99

10 **2,3,4,5-Tetrahydro-1-((1H-imidazol-4-ylmethyl)-8-(((4-methylphenyl)sulfonyl)amino)-3-(phenylmethyl)-1H-1,4-benzodiazepine-4-carboxylic acid, 1,1-dimethylethylester.**

p-Toluenesulfonyl chloride (0.054 g, 0.34 mmol) was added to a solution of 8-amino-2,3,4,5-tetrahydro-1-((1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine-4-carboxylic acid, 1,1-dimethylethyl ester (prepared as described in Compound E of Example 98, 0.125 g, 0.28 mmol) and triethylamine (0.048 mL, 0.34 mmol) in CH_2Cl_2 (1 mL) at 0°C under argon. After stirring for 16 hr, the mixture was concentrated and the residue was treated with 1N NaOH (0.6 mL) and MeOH (1 mL). After stirring for 30 min, the reaction mixture was diluted with CHCl_3 (5 mL) and NaHCO_3 (3 mL). The layers were separated and the aqueous layer was reextracted with CHCl_3 (2 x 20 mL). The combined organic layers were washed with water (1 x 5 mL), brine (1 x 5 mL), dried over MgSO_4 , filtered and concentrated to afford Example 99 (0.15 g, 89%) as a light yellow solid.
25 MS $(\text{M}+\text{H})^+ 588$

Exempl 100

5 **7-Bromo-1,2,3,4-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-5H-1,4-benzodiazepin-5-one, dihydrochloride.**

A. **7-Bromo-2,3,4,5-Tetrahydro-3-(phenylmethyl)-1H-1,4-benzodiazepin-5-one**

10 To a suspension of 0.5 g (1.45 mmoles) of Compound A of Example 75 in 5 mL of THF at rt and under argon, was added 3 mL (3 mmol) of 1 M borane in THF. A clear, bright yellow solution was obtained on addition. Stirring was continued overnight, after which an additional 2 mL (2 mmol) of 1 M borane in THF was added and stirring was continued an
15 additional 8 hr. After hydrolysis of excess borane by the dropwise addition of methanol, the reaction was evaporated to dryness and the residue dissolved in 0.5 mL each of methanol and conc HCl. The resulting solution was heated at reflux for 2 hr, cooled to rt and evaporated to dryness. The residue was evaporated from methanol an additional three times, dissolved in ethyl
20 acetate and the solution washed with brine, dried, and the solvent removed to afford a viscous yellow oil. Flash chromatography on silica gel, with 50% ethyl acetate - hexane gave 205 mg (0.62 mmole, 43 %) of Compound A as a white solid.

25 **B. 7-Bromo-1,2,3,4-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-5H-1,4-benzodiazepin-5-one, dihydrochloride**

 Example 100 was prepared as a nearly white solid in 60% yield from Compound A as described for Compound D of Example 1, with purification by preparative HPLC (gradient of aqueous methanol with 0.1%
30 TFA) and conversion to the HCl salt by treatment with HCl-MeOH.

MS (M+H)⁺ 411

Analysis calculated for C₂₀H₁₉N₄OBr • 0.5 C₂H₁₀O • 1.5 HCl.

Calc'd: C, 52.53; H, 5.11 N, 11.14.

Found: C, 52.82; H, 4.71; N, 11.52.

5

Examples 101-201

The coupling of each carboxylic acid to Compound B of Example 33 was carried out using standard HOAt / DIC mediated coupling. The process was automated by using a Hamilton 2200 Liquid Handler. A Zymark Benchmate[®] robotic workstation was used to carry out the weighings of the test tubes and for purification of the resulting amide products. An IBM PC was used to run the Zymark Benchmate[®] workstation operating program and to write the Benchmate[®] procedures. The standard protocol for preparation of amides is illustrated by the following examples:

A 16 x 100 mm tube was charged with the appropriate carboxylic acid (0.10 mmol, 1.0 eq) and the Liquid Handler then carried out the following steps on the tube:

- 1) Added 0.5 mL of a 0.2 M 1-hydroxy-7-aza-benzotriazole (HOAt) solution in DMF
- 2) Added 0.5 mL of Compound B of Example 33 (0.2 M, 0.10 mmol, 1.0 eq) in DMF
- 3) Added 1.0 mL of a methylene chloride solution of diisopropylcarbodiimide (0.016 mL, 0.10 mmol, 1.0 eq)
- 4) Mixed tube contents by vortexing at speed 3 for 30 sec.

After 24 hr, the mixture was concentrated on a Savant Speed Vac (approx. 2 mm Hg for 72 hr). The residue was purified by ion exchange chromatography on a solid phase extraction cartridge mediated by the

Benchmate[®] robotic workstation using the following protocol:

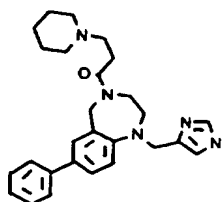
- 1) Added 5.0 mL of methanol/methylene chloride(1:1) to the reaction
- 2) Mixed tube contents by vortexing at speed 3 for 60 sec
- 3) Conditioned a Varian solid phase extraction column (1.5 g, SCX cation exchange) with 10 mL of methanol/methylene chloride at 0.15 mL/sec
- 4) Loaded reaction contents onto column at 0.02 mL/sec
- 5) Washed column with 2 x 7.5 mL of methanol/methylene chloride(1:1) at 0.1 mL/s c

- 6) Washed column with 1 x 7.5 mL of methanol at 0.1 mL/sec
 - 7) Washed column with 0.01 M ammonia in methanol
 - 8) Eluted column with 7.5 mL of 1 M ammonia in methanol and collect into a tared receiving tube at 0.05 mL/sec.
- 5 All solution/solvent deliveries were followed by 1.0 mL of air and a 5 sec push delay was used after loading reaction contents onto the ion exchange column. The product solution was concentrated on a Savant Speed Vac (approx. 2 mm Hg for 20 hr) to afford the target compound.
- Syntheses requiring further purification were subjected to preparative HPLC
- 10 (YMC S3 ODS 50X100 mm, 30 mL/min, 10 minute gradient of 10-90% aqueous methanol with 0.1%TFA, monitored at 220 nm). The appropriate fractions were combined and concentrated under vacuum. The residues were dissolved in methanol (5 mL) and 1N HCl (1 mL) and concentrated on a Savant Speed Vac (approx. 2 mm Hg for 20 hr) to afford the target
- 15 compound. Target compounds were characterized by analytical HPLC and mass spectrometry.

Exemplar Structure

Mass Spectrum

101

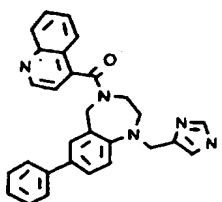


2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[1-oxo-3-(1-piperidinyl)propyl]-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride.

m/z 444

(M+H)

102

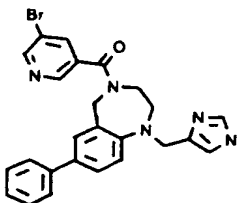


2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-(4-quinolinylcarbonyl)-1H-1,4-benzodiazepine, trihydrochloride.

m/z 460

(M+H)

103

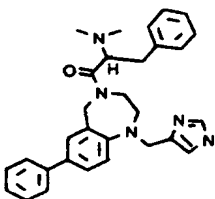


4-[(5-Bromo-3-pyridinyl)carbonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride.

m/z 489

(M+H)

104

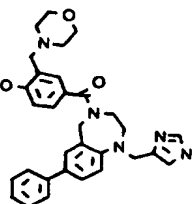


(S)-4-[2-(Dimethylamino)-1-oxo-3-phenylpropyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride.

m/z 480

(M+H)

105

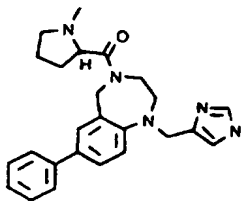


2,3,4,5-Tetrahydro-4-[4-hydroxy-3-(4-morpholinylmethyl)benzoyl]-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride.

m/z 524

(M+H)

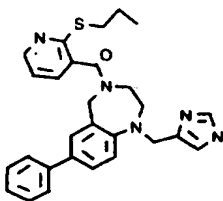
106



(S)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[(1-methyl-2-pyrrolidinyl)carbonyl]-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride.

m/z 416
(M+H)

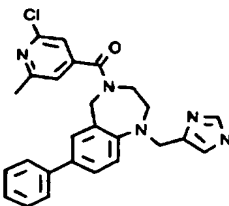
107



2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-[[2-(propylthio)-3-pyridinyl]carbonyl]-1H-1,4-benzodiazepine, trihydrochloride.

m/z 484
(M+H)

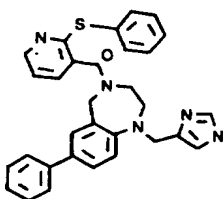
108



4-[(2-Chloro-6-methyl-4-pyridinyl)carbonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride.

m/z 458
(M+H)

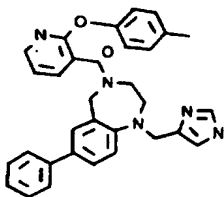
109



2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-[[2-(phenylthio)-3-pyridinyl]carbonyl]-1H-1,4-benzodiazepine, trihydrochloride.

m/z 518
(M+H)

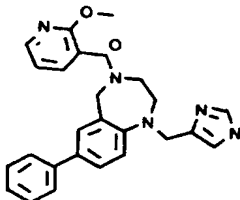
110



2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[[2-(4-methylphenoxy)-3-pyridinyl]carbonyl]-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride.

m/z 516
(M+H)

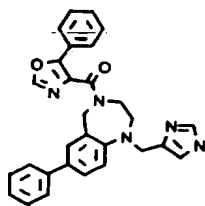
111



2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[(2-methoxy-3-pyridinyl)carbonyl]-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride.

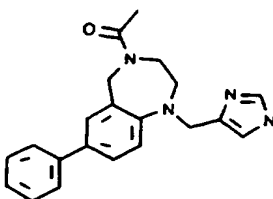
m/z 440
(M+H)

112



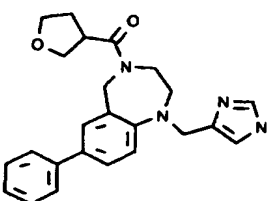
2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl- (M+H)
4-[(5-phenyl-4-oxazolyl)carbonyl]-1H-1,4-benzodiazepine,
dihydrochloride.

113



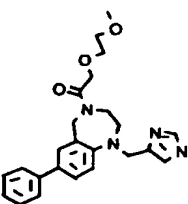
4-Acetyl-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine,
dihydrochloride.

114



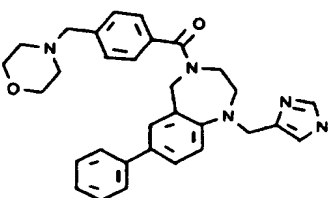
2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl- (M+H)
4-[(tetrahydro-3-furanyl)carbonyl]-1H-1,4-benzodiazepine,
dihydrochloride.

115



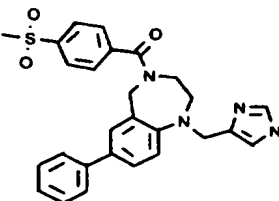
2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[(2-methoxyethoxy)acetyl]-7-phenyl-1H-1,4-benzodiazepine,
dihydrochloride.

116



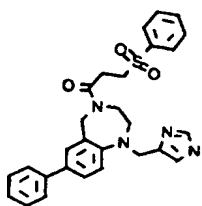
2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[4-(4-morpholinylmethyl)benzoyl]-7-phenyl-1H-1,4-benzodiazepine,
trihydrochloride.

117



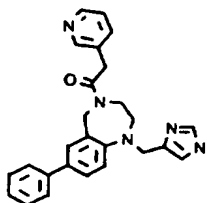
2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[4-(methylsulfonyl)benzoyl]-7-phenyl-1H-1,4-benzodiazepine,
dihydrochloride.

118



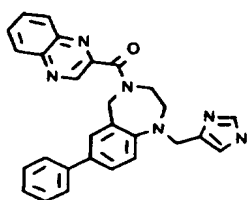
2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[1-oxo-3-(phenylsulfonyl)propyl]-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride. m/z 501 (M+H)

119



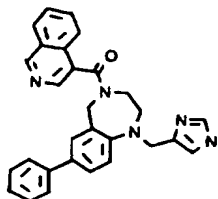
2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-(3-pyridinylacetyl)-1H-1,4-benzodiazepine, trihydrochloride. m/z 424 (M+H)

120



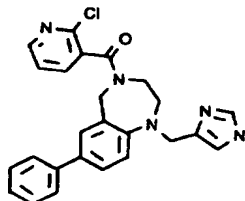
2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-(2-quinoxalinylylcarbonyl)-1H-1,4-benzodiazepine, tetrahydrochloride. m/z 461 (M+H)

121



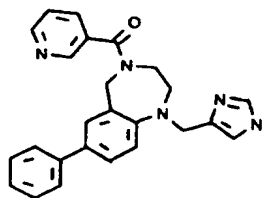
2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(4-isoquinolinylcarbonyl)-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride. m/z 460 (M+H)

122



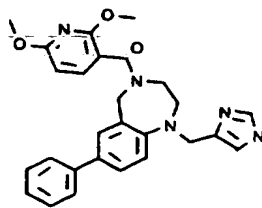
4-[(2-Chloro-3-pyridinyl)carbonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride. m/z 444 (M+H)

123



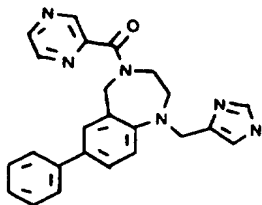
2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-(3-pyridinylcarbonyl)-1H-1,4-benzodiazepine, trihydrochloride. m/z 410 (M+H)

124



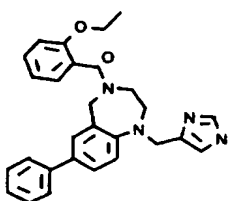
4-[(2,6-Dimethoxy-3-pyridinyl)carbonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride. m/z 470 (M+H)

125



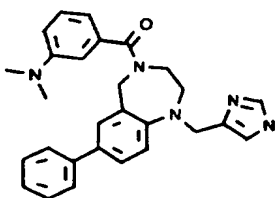
2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-(2-pyrazinylcarbonyl)-1H-1,4-benzodiazepine, tetrahydrochloride. m/z 411 (M+H)

126



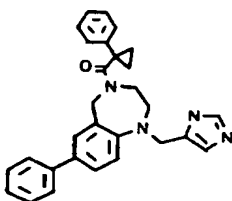
4-(2-Ethoxybenzoyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride. m/z 453 (M+H)

127



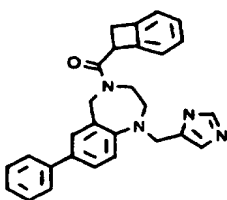
4-[3-(Dimethylamino)benzoyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride. m/z 452 (M+H)

128

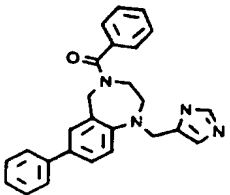
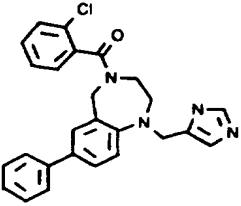
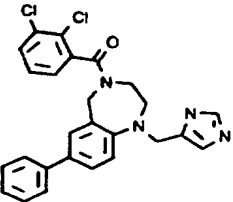
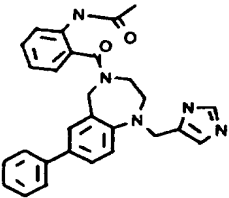
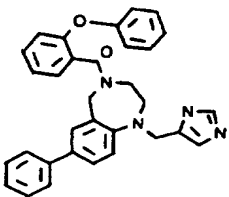
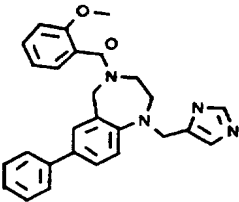
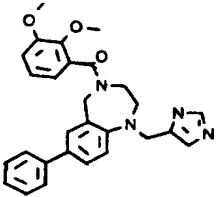


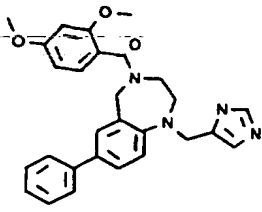
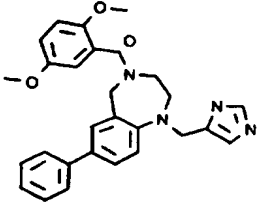
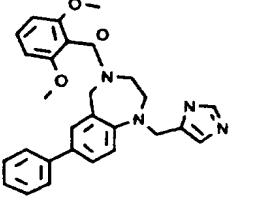
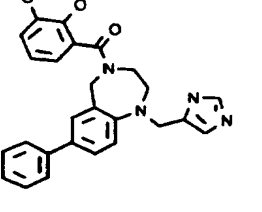
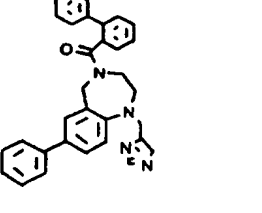
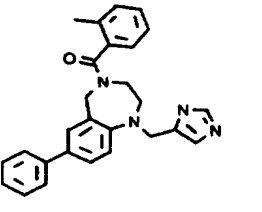
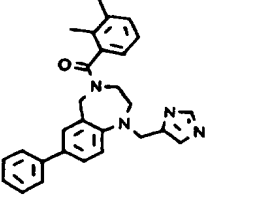
2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-[(1-phenylcyclopropyl)carbonyl]-1H-1,4-benzodiazepine, dihydrochloride. m/z 449 (M+H)

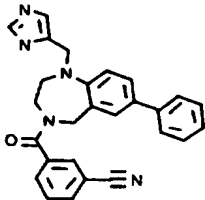
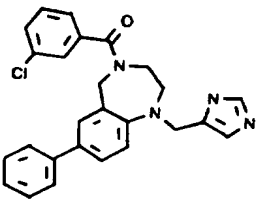
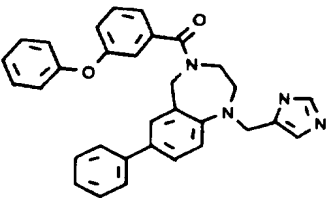
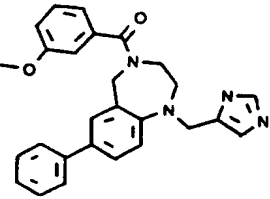
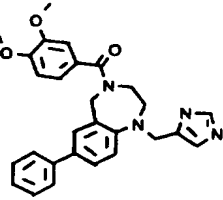
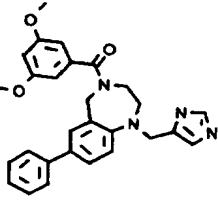
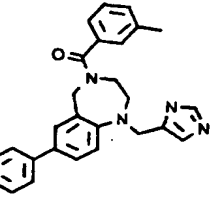
129

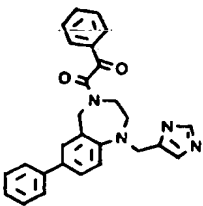
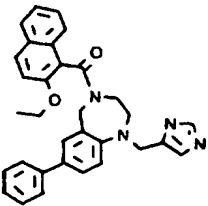
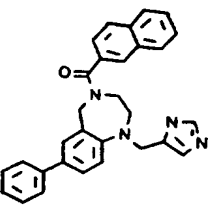
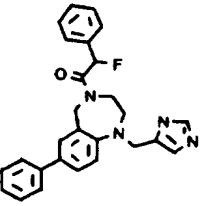
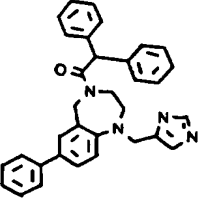
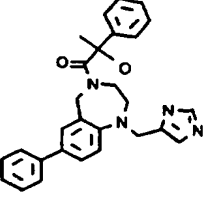
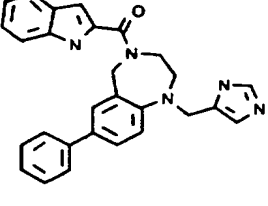


4-[(Bicyclo[4.2.0]octa-1,3,5-trien-7-yl)carbonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride. m/z 435 (M+H)

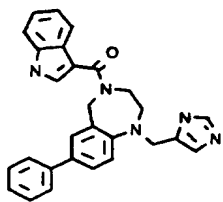
- 130  4-Benzoyl-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride. m/z 409 (M+H)
- 131  4-(2-Chlorobenzoyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride. m/z 443 (M+H)
- 132  4-(2,3-Dichlorobenzoyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride. m/z 478 (M+H)
- 133  N-[2-[[2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepin-4-yl]carbonyl]phenyl]-acetamide, dihydrochloride. m/z 466 (M+H)
- 134  2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(2-phenoxybenzoyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride. m/z 501 (M+H)
- 135  2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(2-methoxybenzoyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride. m/z 439 (M+H)
- 136  4-(2,3-Dimethoxybenzoyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride. m/z 469 (M+H)

- 137  4-(2,4-Dimethoxybenzoyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride. m/z 469 (M+H)
- 138  4-(2,5-Dimethoxybenzoyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride. m/z 469 (M+H)
- 139  4-(2,6-Dimethoxybenzoyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride. m/z 469 (M+H)
- 140  4-(2,3-Dihydroxybenzoyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride. m/z 439 (M-H)
- 141  4-([1,1'-Biphenyl]-2-ylcarbonyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride. m/z 485 (M+H)
- 142  2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(2-methylbenzoyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride. m/z 423 (M+H)
- 143  4-(2,3-Dimethylbenzoyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride. m/z 437 (M+H)

- 144  4-(3-Cyanobenzoyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride. m/z 434 (M+H)
- 145  4-(3-Chlorobenzoyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride. m/z 443 (M+H)
- 146  2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(3-phenoxybenzoyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride. m/z 501 (M+H)
- 147  2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(3-methoxybenzoyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride. m/z 439 (M+H)
- 148  4-(3,4-Dimethoxybenzoyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride. m/z 469 (M+H)
- 149  4-(3,5-Dimethoxybenzoyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride. m/z 469 (M+H)
- 150  2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(3-methylbenzoyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride. m/z 423 (M+H)

- 151  4-(1,2-Dioxo-2-phenylethyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride. m/z 437 (M+H)
- 152  4-[(2-Ethoxy-1-naphthalenyl)carbonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride. m/z 503 (M+H)
- 153  2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(2-naphthalenylcarbonyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride. m/z 459 (M+H)
- 154  4-(Fluorophenylacetyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride. m/z 441 (M+H)
- 155  4-(Diphenylacetyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride. m/z 499 (M+H)
- 156  2,3,4,5-Tetrahydro-4-(2-hydroxy-1-oxo-2-phenylpropyl)-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride. m/z 453 (M+H)
- 157  2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1H-indol-2-ylcarbonyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride. m/z 448 (M+H)

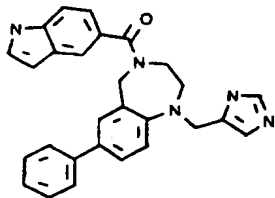
158



2,3,4,5-Tetrahydro-1-(1H-indol-3-ylmethyl)-4-(1H-indol-3-ylcarbonyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride.

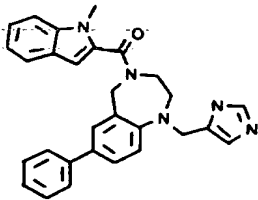
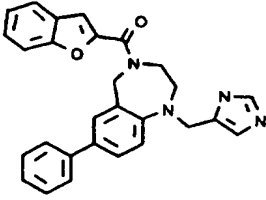
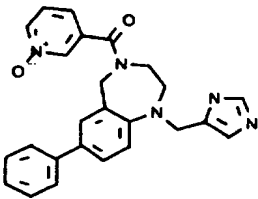
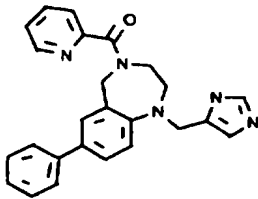
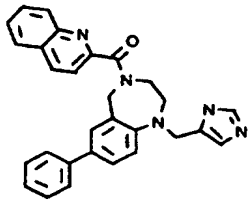
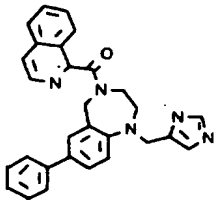
m/z 448
(M+H)

159

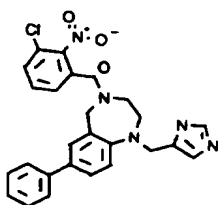


2,3,4,5-Tetrahydro-1-(1H-indol-5-ylmethyl)-4-(1H-indol-5-ylcarbonyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride.

m/z 448
(M+H)

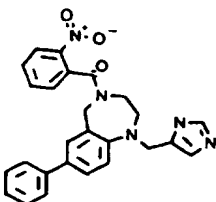
- 160  2,3,4,5-Tetrahydro-1-(1H-m/z 462
imidazol-4-ylmethyl)-4- (M+H)
[(1-methyl-1H-indol-2-
yl)carbonyl]-7-phenyl-1H-
1,4-benzodiazepine,
dihydrochloride.
- 161  4-(2- m/z 449
Benzofuranylcabonyl)- (M+H)
2,3,4,5-tetrahydro-1-(1H-
imidazol-4-ylmethyl)-7-
phenyl-1H-1,4-
benzodiazepine,
dihydrochloride.
- 162  2,3,4,5-Tetrahydro-1-(1H-m/z 426
imidazol-4-ylmethyl)-7- (M+H)
phenyl-4-(3-
pyridinylcarbonyl)-1H-
1,4-benzodiazepine, N-
oxide, dihydrochloride.
- 163  2,3,4,5-Tetrahydro-1-(1H-m/z 410
imidazol-4-ylmethyl)-7- (M+H)
phenyl-4-(2-
pyridinylcarbonyl)-1H-
1,4-benzodiazepine,
trihydrochloride.
- 164  2,3,4,5-Tetrahydro-1-(1H-m/z 460
imidazol-4-ylmethyl)-7- (M+H)
phenyl-4-(2-
quinolinylcarbonyl)-1H-
1,4-benzodiazepine,
trihydrochloride.
- 165  2,3,4,5-Tetrahydro-1-(1H-m/z 460
imidazol-4-ylmethyl)-7- (M+H)
phenyl-4-(1-
isoquinolinylcarbonyl)-
1H-1,4-benzodiazepine,
trihydrochloride.

166



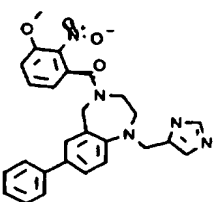
4-(3-Chloro-2-nitrobenzoyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride. m/z 488 (M+H)

167



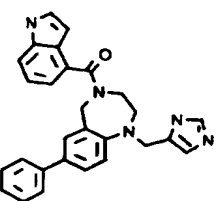
2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(2-nitrobenzoyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride. m/z 454 (M+H)

168



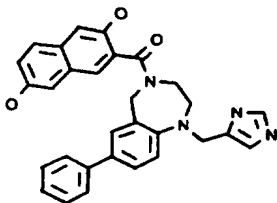
2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(3-methoxy-2-nitrobenzoyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride. m/z 484 (M+H)

169



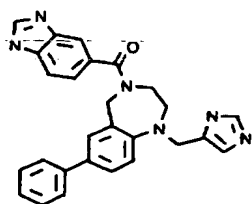
2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1H-indol-4-ylcarbonyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride. m/z 448 (M+H)

170



4-[(2,6-Dihydroxy-3-naphthalenyl)carbonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride. m/z 491 (M+H)

171

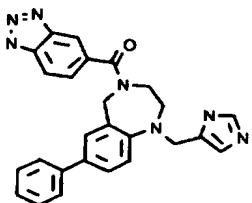


4-(1H-Benzimidazol-5-ylcarbonyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride.

m/z 449

(M+H)

172

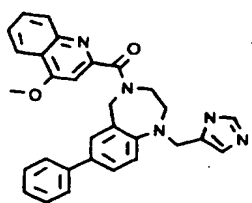


4-(1H-Benzotriazol-5-ylcarbonyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride.

m/z 450

(M+H)

173

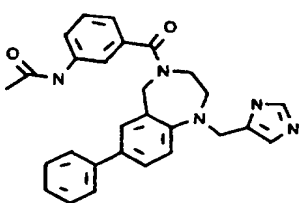


2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-phenyl-1H-1,4-benzodiazepine, trihydrochloride.

m/z 490

(M+H)

174

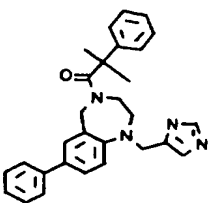


N-[3-[[2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepin-4-yl]carbonyl]phenyl]-acetamide, dihydrochloride.

m/z 466

(M+H)

175

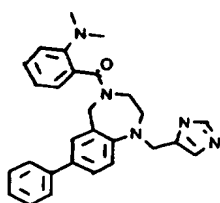


2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(2-methyl-1-oxo-2-phenylpropyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride.

m/z 451

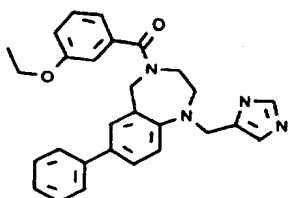
(M+H)

176



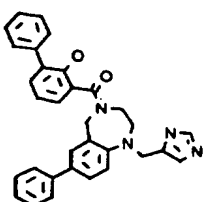
4-[2-
(Dimethylamino)benzoyl]-(M+H)
2,3,4,5-tetrahydro-1-(1H-
imidazol-4-ylmethyl)-7-
phenyl-1H-1,4-
benzodiazepine,
trihydrochloride.

177



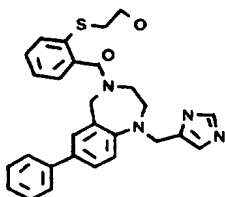
4-(3-Ethoxybenzoyl)- m/z 453
2,3,4,5-tetrahydro-1-(1H- (M+H)
imidazol-4-ylmethyl)-7-
phenyl-1H-1,4-
benzodiazepine,
dihydrochloride.

178



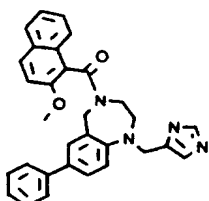
2,3,4,5-Tetrahydro-4-(2- m/z 501
hydroxy[1,1'-biphenyl]-3- (M+H)
ylcarbonyl)-1-(1H-
imidazol-4-ylmethyl)-7-
phenyl-1H-1,4-
benzodiazepine,
dihydrochloride.

179



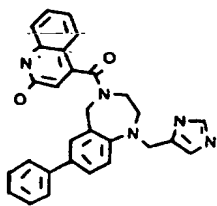
2,3,4,5-Tetrahydro-4-[2- m/z 485
[(2- (M+H)
hydroxyethyl)thio]benzoyl
]-1-(1H-imidazol-4-
ylmethyl)-7-phenyl-1H-
1,4-benzodiazepine,
dihydrochloride.

180



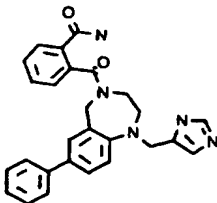
2,3,4,5-Tetrahydro-1-(1H- m/z 489
imidazol-4-ylmethyl)-4- (M+H)
[(2-methoxy-1-
naphthalenyl)carbonyl]-7-
phenyl-1H-1,4-
benzodiazepine,
dihydrochloride.

181



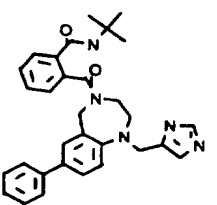
2,3,4,5-Tetrahydro-4-[(2- m/z 476
hydroxy-4-quinolinyl)- (M+H)
carbonyl]-1-(1H-imidazol-
4-ylmethyl)-7-phenyl-1H-
1,4-benzodiazepine,
dihydrochloride.

182



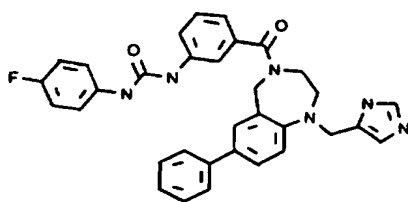
2-[[2,3,4,5-Tetrahydro-1- m/z 452
(1H-imidazol-4-ylmethyl)- (M+H)
7-phenyl-1H-1,4-
benzodiazepin-4-
yl]carbonyl]benzamide,
dihydrochloride.

183



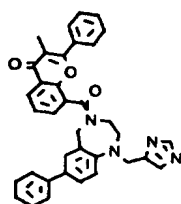
N-(1,1-Dimethylethyl)-2- m/z 508
[[2,3,4,5-tetrahydro-1- (M+H)
(1H-imidazol-4-ylmethyl)-
7-phenyl-1H-1,4-
benzodiazepin-4-
yl]carbonyl]benzamide,
dihydrochloride.

184



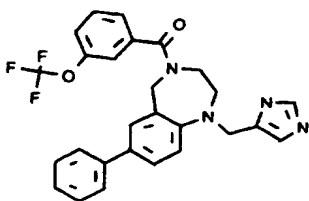
N-(4-Fluorophenyl)-N'-[3- m/z 561
[[2,3,4,5-tetrahydro-1- (M+H)
(1H-imidazol-4-ylmethyl)-
7-phenyl-1H-1,4-
benzodiazepin-4-
yl]carbonyl]phenyl]urea,
dihydrochloride.

185



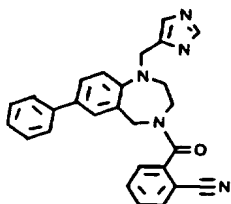
2,3,4,5-Tetrahydro-1-(1H-m/z 567
imidazol-4-ylmethyl)-4- (M+H)
[(3-methyl-4-oxo-2-
phenyl-4H-benzopyran-
8-yl)carbonyl]-7-phenyl-
1H-1,4-benzodiazepine,
dihydrochloride.

186



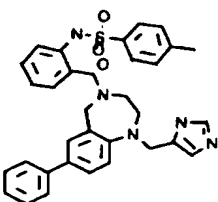
2,3,4,5-Tetrahydro-1-(1H-m/z 493
imidazol-4-ylmethyl)-7-phenyl-4-[3-
(trifluoromethoxy)benzoyl]
]-1H-1,4-benzodiazepine,
dihydrochloride.

187



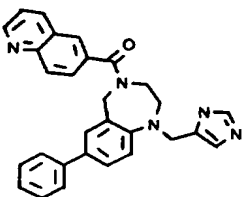
4-(2-Cyanobenzoyl)-m/z 434
2,3,4,5-tetrahydro-1-(1H- (M+H)
imidazol-4-ylmethyl)-7-
phenyl-1H-1,4-
benzodiazepine,
dihydrochloride.

188



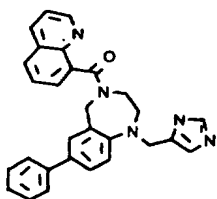
2,3,4,5-Tetrahydro-1-(1H-m/z 578
imidazol-4-ylmethyl)-4-[2-(M+H)
[[4-
methylphenyl)sulfonyl]am
ino]
benzoyl]-7-phenyl-1H-
1,4-benzodiazepine,
dihydrochloride.

189



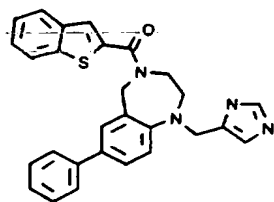
2,3,4,5-Tetrahydro-1-(1H-m/z 460
imidazol-4-ylmethyl)-7-phenyl-4-(6-
quinolinylcarbonyl)-1H-
1,4-benzodiazepine,
trihydrochloride.

190



2,3,4,5-Tetrahydro-1-(1H-m/z 460
imidazol-4-ylmethyl)-7-phenyl-4-(8-
quinolinylcarbonyl)-1H-
1,4-benzodiazepine,
trihydrochloride.

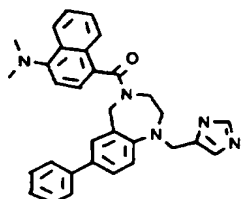
191



4-(Benzo[b]thiophen-2-ylcarbonyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride.

m/z 465
(M+H)

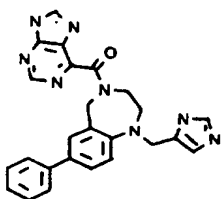
192



4-[[4-(Dimethylamino)-1-naphthalenyl]carbonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride.

m/z 502
(M+H)

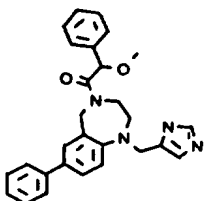
193



2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-(1H-purin-6-ylcarbonyl)-1H-1,4-benzodiazepine, trihydrochloride.

m/z 449
(M-H)

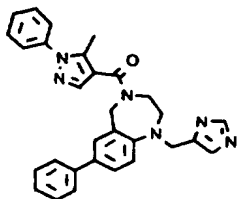
194



2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methoxyphenylacetyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride.

m/z 453
(M+H)

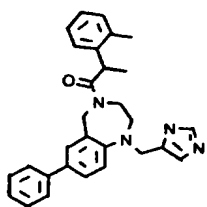
195



2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[(5-methyl-1-phenyl-1H-pyrazol-4-yl)carbonyl]-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride.

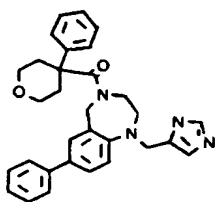
m/z 489
(M+H)

196



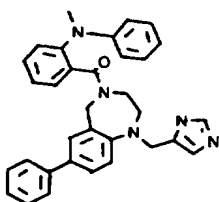
2,3,4,5-Tetrahydro-1-(1H-m/z 451
imidazol-4-ylmethyl)-4-[2-(M+H)
(2-methylphenyl)-1-
oxopropyl]-7-phenyl-1H-
1,4-benzodiazepine,
dihydrochloride.

197



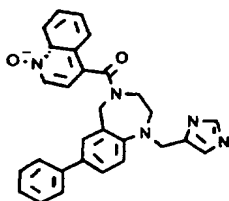
2,3,4,5-Tetrahydro-1-(1H-m/z 493
imidazol-4-ylmethyl)-7- (M+H)
phenyl-4-[(tetrahydro-4-
phenyl-2H-pyran-4-
yl)carbonyl]-1H-1,4-
benzodiazepine,
dihydrochloride.

198



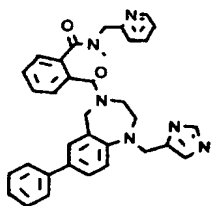
2,3,4,5-Tetrahydro-1-(1H-m/z 531
imidazol-4-ylmethyl)-4-[2-(M+18)
(methylphenylamino)ben
zoyl]-7-phenyl-1H-1,4-
benzodiazepine,
trihydrochloride.

199



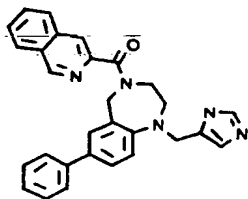
2,3,4,5-Tetrahydro-1-(1H-m/z 476
imidazol-4-ylmethyl)-7- (M+H)
phenyl-4-(4-
quinolinylnylcarbonyl)-1H-
1,4-benzodiazepine, N-
oxide, dihydrochloride.

200



N-Methyl-N-(2- m/z 557
pyridinylmethyl)-2- (M+H)
[[2,3,4,5-tetrahydro-1-
(1H-imidazol-4-ylmethyl)-
7-phenyl-1H-1,4-
benzodi-azepin-4-
yl]carbonyl]benzamide,
trihydrochloride.

201



2,3,4,5-Tetrahydro-1-(1H-m/z 460
imidazol-4-ylmethyl)-4-(3-(M+H)
isoquinolinylcarbonyl)-7-
phenyl-1H-1,4-
benzodiazepine,
trihydrochloride.

Examples 202-219

- To a mixture of compound Compound A of Example 4 (3.83 g, 15.4 mmol) and 4-imidazolecarboxaldehyde (2.22g, 23.1 mmol) in 120 mL of CH₂Cl₂ and 3 mL of AcOH at room temperature was added NaBH(OAc)₃ (4.89 g, 23.1 mmol). The mixture was stirred for 1.5 hours, diluted with 200 mL of CH₂Cl₂, and washed with 5% NaHCO₃. The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo. Flash chromatography of the residue on silica (eluting with 5% MeOH/CH₂Cl₂ and trace NH₄OH) afforded 2.01 g (40%) of 2,3,4,5-tetrahydro-4-[(1,1-dimethylethoxy)-carbonyl]-1-(1H-imidazol-4-yl-methyl)-1H-1,4-benzodiazepine. An additional 0.42 g (8%) of product was obtained by stirring 1.5 g of a high R_f material in 1:1:1 THF/MeOH/NH₄OH, followed by extraction with EtOAc, and flash chromatography.
- Hydroxymethyl resin (3.5 g, 6.58 mmol, 1.88 mmol/g) was swelled with 50 mL of 1,2-dichloroethane for 45 min at room temperature in a 125 mL shake flask. To this was added paraformaldehyde (0.15 g, 5.0 mmol). HCl (g) was bubbled through the mixture for 15 min. Then, an additional amount of paraformaldehyde (0.15 g, 5.0 mmol) was added to the reaction mixture. HCl (g) was bubbled through the mixture with shaking for 4h. The 1,2-dichloroethane was removed and the resin was rinsed with 1,2-dichloroethane (4 x 20 mL).
- The resin was suspended in 20 mL of 1,2-dichloroethane and then treated with a solution of 2,3,4,5-tetrahydro-4-[(1,1-dimethylethoxy)-carbonyl]-1-(1H-imidazol-4-yl-methyl)-1H-1,4-benzodiazepine (2.23 g, 6.78 mmol) in 25 mL of 1,2-dichloroethane and 6 mL of DIEA. The mixture was shaken at room temperature for 12 h. MeOH (2 mL) was added and the mixture was shaken for an additional 1.5 h. The solvent was removed and the resin was rinsed sequentially with 1,2-dichloroethane (2 x 20 mL), DMF (2 x 20 mL), and MeOH (2 x 20 mL). The material was dried in vacuo to afford 4.58 g (67%) of resin containing imidazole-bound 2,3,4,5-tetrahydro-4-[(1,1-dimethylethoxy)-carbonyl]-1-(1H-imidazol-4-yl-methyl)-1H-1,4-benzodiazepine (%N=4.39). To 150 mg (0.135 mmol, 0.90 mmol/g) of this resin in a 5 mL polypropylene syringe barrel was added 1.5 mL of 3% Et₃SiH in CH₂Cl₂ and 0.5 mL of TFA. The tube was placed in a vac-elute chamber (capacity for 24 syringe barrels) and the entire apparatus was shaken on an orbital shaker for 3 h. The solvent was removed and the resin was rinsed sequentially with 2 mL

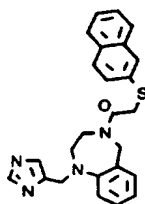
- each of CH₂Cl₂, 25% Et₃N/CH₂Cl₂, MeOH, DMF, and CH₂Cl₂. The resin was swelled with 0.5 mL of a DMF solution containing 1M DIEA and 0.5M HOBT. To this was added 50 mg of carboxylic acid, followed by 1.5 mL of a CH₂Cl₂ solution containing 0.2M EDC. The mixture was shaken for 18 h.
- 5 The solvent was removed and the resin was rinsed sequentially with 2 mL each of CH₂Cl₂, 25% Et₃N/CH₂Cl₂, MeOH, DMF, and CH₂Cl₂. The coupling procedure was repeated. The products were cleaved from the resin by shaking for 18 h in the presence of a HBr/TFA/thioanisole solution (prepared by mixing 45 mL of TFA, 1.25 mL of thioanisole, and 5 mL of 30% HBr/HOAc). The solvent was removed and the resin was rinsed with MeOH (3 x 3 mL). The solvent was removed in vacuo, and the residue was purified by HPLC (C18, 50 x 100mm, 10%-90% MeOH with 0.1% TFA, 10 min gradient, 20 mL/min). Target compounds were characterized by analytical HPLC and mass spectrometry.

15

Example Structure

Mass Spectrum

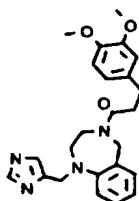
202



2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[(2-naphthalenylthio)acetyl]-1H-1,4-benzodiazepine, trifluoroacetate (1:2)

m/z 429
(M+H)

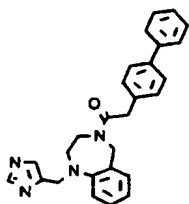
203



4-[3-(3,4-Dimethoxyphenyl)-1-oxopropyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate (1:2).

m/z 421
(M+H)

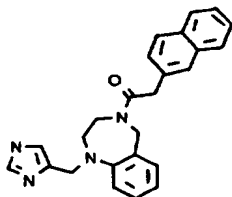
204



4-[(1,1'-Biphenyl)-4-ylacetyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate (1:2).

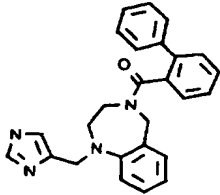
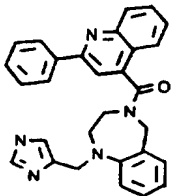
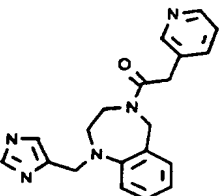
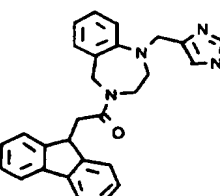
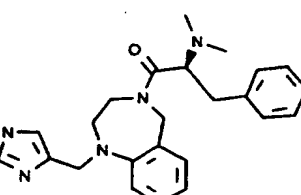
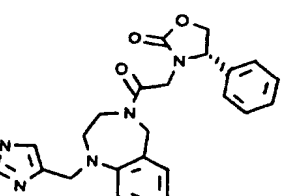
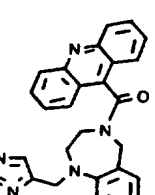
m/z 423
(M+H)

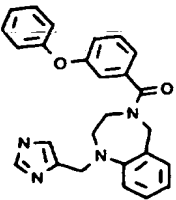
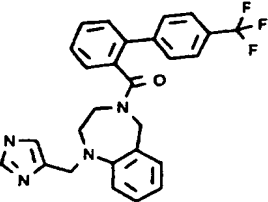
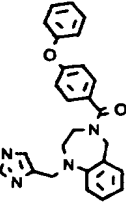
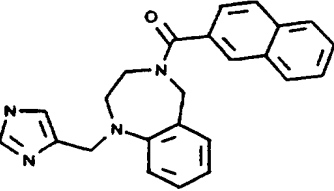
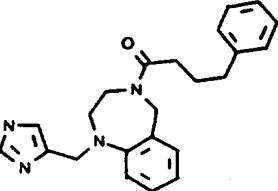
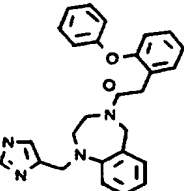
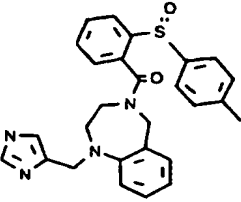
205



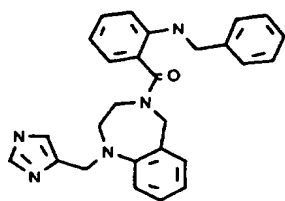
2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(2-naphthalenylacetyl)-1H-1,4-benzodiazepine, trifluoroacetate (1:2).

m/z 397
(M+H)

- 206  4-([1,1'-Biphenyl]-2-ylcarbonyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate (1:2). m/z 409 (M+H)
- 207  2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[(2-phenyl-(M+H) 4-quinoliny)carbonyl]-1H-1,4-benzodiazepine, trifluoroacetate (1:3). m/z 460
- 208  2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(3-pyridinylacetyl)-1H-1,4-benzodiazepine, trifluoroacetate (1:3). m/z 348 (M+H)
- 209  4-(9H-Fluoren-9-ylacetyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate (1:2). m/z 435 (M+H)
- 210  Chiral (S)-4-[2-(Dimethylamino)-1-oxo-3-phenylpropyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate (1:3). m/z 404 (M+H)
- 211  (S)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[(2-oxo-4-phenyl-3-oxazolidinyl)acetyl]-1H-1,4-benzodiazepine, trifluoroacetate (1:2). m/z 432 (M+H)
- 212  4-(9-Acridinylcarbonyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate (1:3). m/z 434 (M+H)

213		2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(3-phenoxybenzoyl)-1H-1,4-benzodiazepine, trifluoroacetate (1:2).	m/z 425 (M+H)
214		2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[[4'-(trifluoromethyl)][1,1'-biphenyl]-2-yl]carbonyl]-1H-1,4-benzodiazepine, trifluoroacetate (1:2).	m/z 477 (M+H)
215		2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(4-phenoxybenzoyl)-1H-1,4-benzodiazepine, trifluoroacetate (1:2).	m/z 425 (M+H)
216		2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(2-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, trifluoroacetate (1:2).	m/z 383 (M+H)
217		2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-oxo-4-phenylbutyl)-1H-1,4-benzodiazepine, trifluoroacetate (1:2).	m/z 375 (M+H)
218		2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[(2-phenoxyphenyl)acetyl]-1H-1,4-benzodiazepine, trifluoroacetate (1:2).	m/z 439 (M+H)
219		2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[2-[(4-methylphenyl)sulfinyl]benzoyl]-1H-1,4-benzodiazepine, trifluoroacetate (1:2)	m/z 471 (M+H)

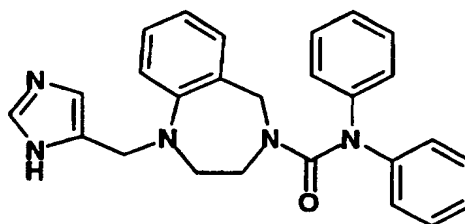
220



2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[2-[(phenylmethyl)amino]benzoyl]-1H-1,4-benzodiazepine, trifluoroacetate (1:3)

m/z 438
(M+H)

Example 221



- 5 **1,2,3,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-N,N-diphenyl-4H-1,4-benzodiazepine-4-carboxamide, hydrochloride.**

Example 221 was prepared as a light yellow solid from N,N-diphenylcarbonyl chloride as described for Example 9.

10 MS (M+H)⁺ 424

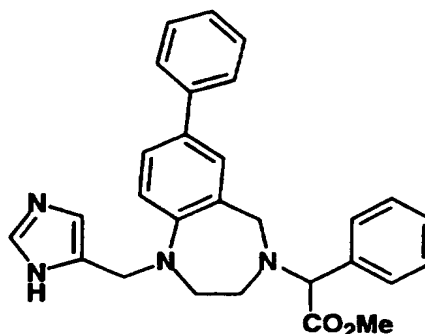
Analysis calculated for C₂₆H₂₅N₅O • 2.2 H₂O • 2.2 HCl.

Calc'd: C, 57.47; H, 5.87; N, 12.89; Cl, 14.35

Found: C, 57.25; H, 5.78; N, 13.25; Cl, 14.73.

15

• Example 222



1,2,3,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-a,7-diphenyl-4H-1,4-benzodiazepine-4-acetic acid, methyl ester, hydrochloride.

20

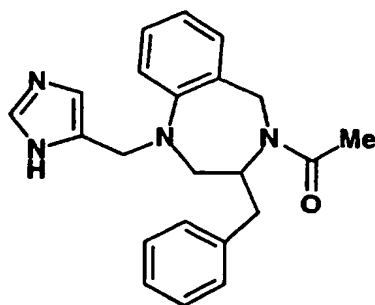
To a stirred suspension of Compound B of Example 12 (220 mg, 1.0 mmol) in MeOH in the presence of solid K_2CO_3 at room temperature under argon was added methyl bromophenylacetate (0.18 mL, 1.1 mmol). The mixture was stirred for 18 h, the solvent was removed, and the residue was purified by flash column chromatography (3:2, hexanes and ethyl acetate) to give 1,2,3,5-tetrahydro- α ,7-diphenyl-4H-1,4-benzodiazepine-4-acetic acid, methyl ester as an oil (220 mg, 63%). This material was reacted as described for Compound D of Example 1 to afford Example 222 as a yellow solid.

MS (M+H)⁺ 453

Analysis calculated for $C_{28}H_{28}N_4O_2 \cdot 0.2 H_2O \cdot 2.5 HCl$.

Calc'd: C, 61.44; H, 5.69; N, 10.24; Cl, 16.19.

Found: C, 61.33; H, 5.88; N, 9.94; Cl, 16.00.

Example 223

5 **4-Acetyl-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, hydrochloride.**

Example 223 was prepared as a tan solid from isatoic anhydride and D,L-phenylalanine-O methyl ester hydrochloride as described for Example 71, except that acetyl chloride (0.25 eq) was used in place of naphthoyl chloride.

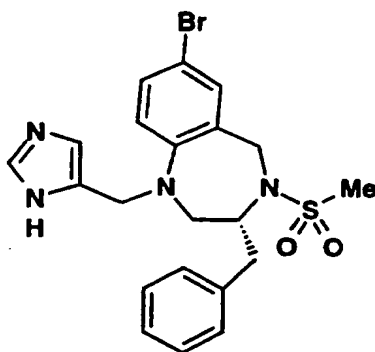
MS (M + H)⁺ 453

Analysis calculated for C₂₂H₂₄N₄O · 1.5 H₂O · 1.2 HCl.

Calc'd: C, 61.74; H, 6.26; N, 13.26; Cl, 9.49.

Found: C, 61.80; H, 6.62; N, 13.10; Cl, 9.12.

15

Example 224

20 **(R)-7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, hydrochloride.**

A. (R)-7-Bromo-2,3,4,5-tetrahydro-3-(phenylmethyl)-1H-1,4-benzodiazepin-2,5-dione

A stirred solution of bromoisatoic anhydride (150 g, 0.62 mol) and D-phenylalanine methyl ester hydrochloride (127.3 g, 0.59 mol) in the presence of 4-dimethylaminopyridine (2 g) in pyridine (1500 mL) was heated at reflux under argon for 3 days. The pyridine was removed in vacuo and the residue was dissolved in methylene chloride (3 L). This solution was washed with 10% HCl solution and brine. The organic solution was dried and concentrated in vacuo to a small volume. The solid thus formed was collected and dried to give 152 g (71%) of Compound A, mp 242-243°C.

B. (R)-7-Bromo-2,3,4,5-tetrahydro-3-(phenylmethyl)-1H-1,4-benzodiazepine

A stirred solution Compound A (30 g, 87 mmol) in anhydrous THF (870 mL) under argon was treated with a solution of borane-tetrahydrofuran complex (440 mL of a 1 M solution, 440 mmol) at room temperature. The solution was slowly heated to reflux and heated at reflux for 18 h. The mixture was cooled to 0°C, and methanol (150 mL) was added to destroy excess of BH₃. The resultant solution was concentrated in vacuo, the residue was dissolved in methanol (250 mL), and 7 N HCl solution (50 mL) was added. This mixture was heated on a steam-bath for 2 h. The solid thus formed was collected, resuspended in water (400 mL) and the aqueous suspension was made basic to pH 11 with 5 N NaOH solution and extracted with ethyl acetate (2 x 300 mL). The organic extracts were combined, dried, concentrated in vacuo and the residue was crystallized from methanol and water (9:1) to give 25 grams of Compound B as a white solid (91%), mp 135-138 °C.

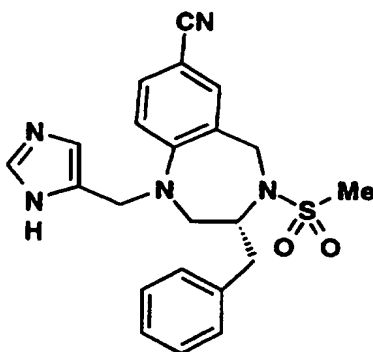
C. (R)-7-Bromo-2,3,4,5-tetrahydro-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine

To a stirred solution of Compound B (1.5 g, 4.73 mmol), pyridine (3 mL), and DIEA (1.6 mL, 9.46 mmol) was added methanesulfonyl chloride (0.55 mL, 7.11 mmol) at 0°C under argon. The resultant mixture was stirred at 0°C for 2 h and 1 N NaOH solution (30 mL) was added. The mixture was stirred for 2 hours and the organic layer was separated, washed with 1 N HCl solution (2 x 100 mL), dried, and concentrated in vacuo to give 1.7 g of Compound C as a yellow solid (91 %).

D. (R)-7-Bromo-2,3,4,5-tetrahydr -1-(1H-imidazol-4-ylm thyl)-4-(methyl ulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiaz pin , hydrochlorid

- 5 To a stirred solution of Compound C (18 g, 45.6 mmol) in acetic acid (50 mL) and dichloroethane (200 mL) at room temperature, was added 4-formylimidazole (6.6 g, 68.5 mmol). The mixture was stirred at room temperature for 30 min. To the resultant solution was added sodium triacetoxymethylborohydride (14.5 g, 68.5 mmol). The mixture was stirred at room temperature for 18 hours, diluted with ethyl acetate (500 mL), cooled to 0°C and made basic to pH 9 with concentrated NH₄OH solution. The mixture was stirred for 2 h and partitioned between ethyl acetate and saturated NaHCO₃ solution. The organic layer was separated and washed with saturated NH₄Cl solution, dried over Na₂SO₄ and concentrated in vacuo. The residue was crystallized from methanol to give a white solid (14 g, 65%). The solid was dissolved in ethyl acetate and 1N HCl solution in ether (60 mL) was added. The solvent was removed in vacuo and the solid was dried in a heated oven under vacuum to give Example 224 as a white solid, mp 180-185 °C.
- 15
- 20 MS (M+H)⁺ 476
[α]_D²⁰: +58° (c = 0.4, MeOH).

Example 225



25

(R)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine-7-carbonitrile, monohydrochloride.

A. (R)-2,3,4,5-Tetrahydro-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine-7-carbonitrile

A stirred solution of Compound C of Example 224 (6.9 g, 17.5 mmol) and copper cyanide (4.0 g, 44 mmol) in N-methylpyrrolidinone (90 mL) was heated at 200°C for 5 h. The mixture was cooled to room temperature and poured into a 10% aqueous solution of ethylene diamine (800 mL). The resultant suspension was stirred at room temperature for 2 h and extracted with ethyl acetate (3 x 150 mL). The combined organic extracts were washed with 5% NH₄OH solution (2 x 100 mL), brine, dried over MgSO₄, and concentrated. The residue was purified by flash chromatography (ethyl acetate, hexanes; 1:1) to give Compound A as a foam (4.5 g, 75%).

B. (R)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine-7-carbonitrile, monohydrochloride

To a stirred solution of Compound A (4.7 g, 13.8 mmol) in acetic acid (30 mL) and dichloroethane (120 mL) at room temperature was added 4-formylimidazole (2.1 g, 22 mmol). The mixture was stirred at room temperature for 30 min. To the resultant solution was added sodium triacetoxyborohydride (4.4 g, 22 mmol). The mixture was stirred at room temperature for 2 h, 4-formylimidazole (1.3 g, 13.5 mmol) was added, the mixture was stirred for 30 min, and sodium triacetoxyborohydride (3.0 g, 14 mmol) was added. This cycle was repeated two times until all starting material was consumed. Workup and product isolation were performed as described for Compound D of Example 224 to provide Example 225 as a white solid (4.1 g, 65%). mp 165°C

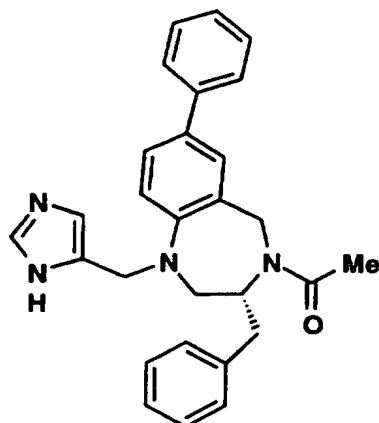
MS (M+H)⁺ 422

[α]_D²⁰: + 218 ° (c = 0.23, MeOH).

Analysis calculated for C₂₂H₂₃N₅O₂S • 1.7 H₂O • 1 HCl.

Calc'd: C, 54.08; H, 5.65; N, 14.33; Cl, 7.26.

Found: C, 54.04; H, 5.38; N, 14.33; Cl, 7.27.

Example 226

5 **(R)-4-Acetyl-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.**

A. 2-Amino-5-phenyl-benzoic acid

10 2-Amino-5-bromo-benzoic acid (30.0 g, 139 mmol), benzenboronic acid (18.6 g, 153 mmol) and K₂CO₃ (48.0 g, 348 mmol) were combined in a mixture of water (300 mL) and THF (300 mL). The mixture was bubbled with Ar vigorously for an hour to degas and a solution of Palladium(II) acetate (2.52 g, 11.2 mmol) in degassed THF (50 mL) was
15 added dropwise over 1h. The mixture was stirred for 16h at room temperature with Ar bubbling. The mixture was concentrated, filtered through a pad of celite and lyophilized to remove water. The lyophilate was triturated with 90% dichloromethane, 10% methanol (500 mL). The filtrate was concentrated and recrystallized from ethyl acetate/hexane to yield
20 Compound A as a brown solid (25g, 84%), MS (M+H)⁺ 214.

B. 6-Phenyl-3,1-oxazine-2,4(1H)-dione

To a solution of Compound A (25.0 g, 0.117 mol) and triphosgene (25.0 g, 0.084 mol) in acetonitrile (250 mL) at 0°C under N₂ was added a
25 solution of triethylamine (3.0 g, 4.1 mL, 0.029 mol) in acetonitrile(50 mL) dropwise over 1 hour. The mixture was stirred at room temperature for 16h and the solid was filtered. The filter cake was washed with dichloromethane and dried under vacuum to yield Compound B as a light brown solid (17.8 g, 63%), MS (M+H)⁺ 241.

C. (R)-2,3,4,5-tetrahydro-7-phenyl-3-(phenylmethyl)-1H-1,4-benzodiazepine

Compound B (9.40 g, 0.0392 mol), D-Phe (6.5 g, 0.0392 mol) and
5 pyridine•HCl (22.6 g, 0.196 mol) were dissolved in pyridine (100 mL). The
solution was refluxed for 4h, cooled and concentrated. The residue was
partitioned between water (200 mL) and ethyl acetate (200mL). The organic
layer was washed with water (3X100mL), brine (50 mL), dried (MgSO₄) and
concentrated to yield compound C as a yellowish glass (6.0 g, 45 %), MS
10 (M+H)⁺ 343.

D. (R)-2,3,4,5-tetrahydro-7-phenyl-3-(phenylmethyl)-1H-1,4-benzodiazepine

Compound C (6.0 g, 0.017 mol) was dissolved in THF (100 mL)
15 and borane (1M in THF, 50 mL, 50 mmol) was added. The solution was
refluxed for 4h and cooled to room temperature. Methanol (50 mL) was
added to quench the residual borane and the solution was concentrated. 1N
HCl (100 mL) was added to the residue and the mixture was refluxed for 4h.
The mixture was cooled to room temperature, acidified to pH 2 with 1N
20 NaOH (110 mL) and extracted with dichloromethane (3X200 mL). The
organic layers were combined, washed with brine (300 mL), dried (Na₂SO₄)
and concentrated to yield compound D as a slightly yellow glass (5.5 g,
99%), MS (M+H)⁺ 315.

E. (R)-4-Acetyl-2,3,4,5-tetrahydro-7-phenyl-3-(phenylmethyl)-1H-1,4-benzodiazepine

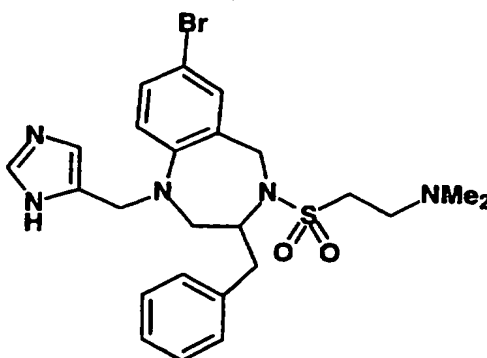
Compound D (5.0 g, 0.016 mol) was dissolved in dichloromethane
(300 mL) and DIEA (2.06 g, 2.8 mL, 0.016 mol) was added at once. A
solution of acetic anhydride (1.46 g, 1.35 mL, 0.0143 mol) in
30 dichloromethane (20 mL) was added dropwise over 30 min. The solution
was stirred for 30 min, washed with saturated sodium bicarbonate (3X100
mL), water (3X100 mL), brine (100 mL), dried (Na₂SO₄) and concentrated to
yield Compound E as a light brown glass (5.0 g, 88%).

F. (R)-4-Acetyl-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride

Compound E (5.0 g, 14.0 mmol) and 4-formylimidazole (4.45 g, 46.3 mmol) were dissolved in 1,2-DCE (100 mL) and acetic acid (50 mL). Sodium triacetoxymethylborohydride (4.45 g, 21.0 mmol) was added all at once and the mixture was stirred at room temperature for 1h. Saturated NaHCO₃ (50 mL) was added followed by ammonium hydroxide (50 mL). The mixture was stirred for 2h, concentrated and the residue was partitioned between water (100 mL) and ethyl acetate (200mL). The organic layer was washed with water (100mL), brine (100 mL), dried (Na₂SO₄), concentrated and chromatographed (silica gel, 5.1 X 15 cm, 95% dichloromethane, 5% methanol) to yield the free base of Example 225 as a brown solid (4.9 g). This brown solid was further purified by preparative HPLC (YMC S-15 ODS column, 50 X 500 mm; solvent A, 0.1% TFA in 90% water, 10 % methanol; solvent B, 0.1% TFA in 10% water, 90% methanol: 20-100% B in 60 min, flow rate 25 mL/min). Fractions containing the desired product were combined, concentrated and lyophilized. This lyophilate was dissolved in acetonitrile (50 mL) and 1N HCl (50 mL). This mixture was concentrated and lyophilized. This procedure is repeated to provide Example 226 as a yellow solid (2.3 g, 35%)

MS (M + H)⁺ 437

¹H-NMR (CD₃OD, 400 MHz) δ (ppm) 8.95 (1H, m), 7.68-7.30 (13H, m), 7.04 (1H, m), 5.21-5.10 (1H, m), 4.78-4.63 (2H, m), 4.63-4.48 (1H, m), 4.38 (1H, m), 3.81-3.76 (1H, m), 3.28-3.15 (1H, m), 2.98-2.93 (1H, m), 2.88-2.80 (1H, m), 2.09 (2H, s), 1.62 (1H, s).

Example 227

5 **7-Bromo-4-[[2-(dimethylamino)ethyl]sulfonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4H-1,4-benzodiazepine, trifluoroacetate (1:2).**

A. 7-Bromo-4-[ethenylsulfonyl]-2,3,4,5-tetrahydro-3-(phenylmethyl)-4H-1,4-benzodiazepine

10 To a mixture of Compound B of Example 224 (250 mg, 0.79 mmol) in THF (20 mL) was added sequentially 2-chloroethane sulfonyl chloride (0.1 mL, 0.95 mmol) and DIEA (0.18 mL, 1.98 mmol). The solution was stirred under argon at room temperature for 18 hours, partitioned between aqueous hydrochloric acid (100 mL, 1 N), and ethyl acetate (100 mL), and extracted
15 with ethyl acetate (2 x 100 mL). The organic layers were combined, dried (MgSO₄) and concentrated in vacuo to provide a crude oil which was purified by flash chromatography (silica, hexane : ethyl acetate 3:1) to provide Compound A as a clear oil (85 mg, 26 %).

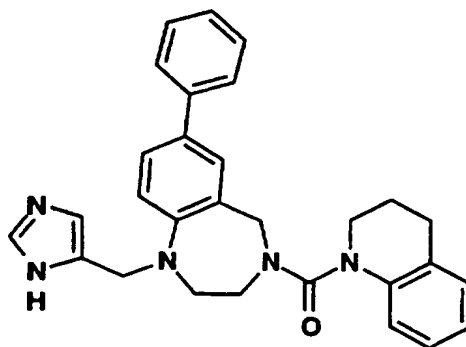
20 **B. 7-Bromo-4-[[2-(dimethylamino)ethyl]sulfonyl]-2,3,4,5-tetrahydro-3-(phenylmethyl)-4H-1,4-benzodiazepine**

To a solution of Compound A (85 mg, 0.21 mmol) in THF (5 mL) was added a solution of dimethylamine (2 mL, 2M in THF). The solution was heated in a sealed pressure bottle at 60°C for 48 hrs, cooled to room
25 temperature and concentrated under vacuum to afford crude Compound B as an oil.

C. 7-Bromo-4-[[2-(dim thylamino)ethyl]sulfonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4H-1,4-benzodiazepine, trifluoroac tate (1:2).

To a stirred solution of Compound B (90 mg, crude, assume 0.21 mmol), 4-formyl imidazole (30 mg, 0.32 mmol), dichloroethane (4 mL) and acetic acid (2 mL) at room temperature was added sodium triacetoxyborohydride (67 mg, 0.32 mmole). The solution was stirred for 48 hour, diluted with ethyl acetate (20 mL) and ammonium hydroxide (5 ml, conc), and stirred for an additional 18 hours. The mixture was extracted with ethyl acetate (2 x 25 mL), and the combined organic extracts were washed with aqueous sodium bicarbonate (25 mL, saturated solution), and then ammonium chloride (25 mL, sat aqueous solution), dried (Na₂SO₄), and concentrated in vacuo to a semi-solid. The crude was purified by preparative HPLC (aqueous methanol gradient containing 0.1% trifluoroacetic acid, C-18 column) and lyophilized to provide Example 227 as a white solid (50 mg, 44 % yield from Compound A), mp 118-120 °C. Analysis calculated for C₂₄H₃₀N₅OSBr • 1.0 H₂O • 2.0 TFA. Calc'd: C, 43.20; H, 4.40; N, 9.00; S, 4.12; Br, 10.26. Found: C, 43.85; H, 4.00; N, 8.35; S, 4.39; Br, 9.43.

Example 228



2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-[(1,2,3,4-tetrahydro-1-quinoliny)carbonyl]-1H-1,4-benzodiazepine, monohydrochloride.

Example 228 was prepared from N-chlorocarbonyl-1,2,3,4-tetrahydroquinoline as described for Example 35, except that the acylation product was chromatographed (silica, 8:2 chloroform: ethyl acetate).

MS (M + H)⁺ 464

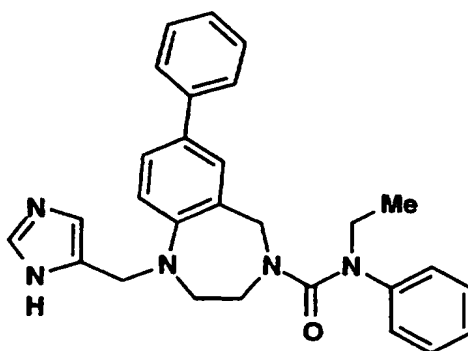
Analysis calculated for C₂₉H₂₉N₅O • 1.0 H₂O • 1.1 HCl • 0.25 ether.

Calc'd: C, 66.70; H, 6.46; N, 12.96; Cl, 7.22.

Found: C, 66.88; H, 6.36; N, 12.62; Cl, 7.30.

5

Example 229



10 **N-Ethyl-1,2,3,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-N,7-diphenyl-4H-1,4-benzodiazepine-4-carboxamide, monohydrochloride.**

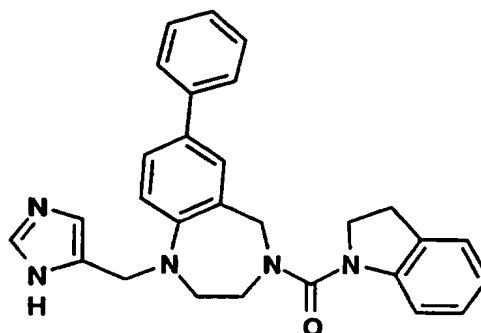
15 Example 229 was prepared from N-chlorocarbonyl-N-ethyl-aniline as described for Example 35. The HCl salt was prepared by dissolving the product in methanol, adding 4N HCl in dioxane, evaporation, redissolving in methanol and precipitating with ether.

MS (M + H)⁺ 452

Analysis calculated for C₂₈H₂₉N₅O • 0.4 H₂O • 1.2 HCl • 0.25 ether.

Calc'd: C, 66.85; H, 6.48; N, 13.44; Cl, 8.16.

20 Found: C, 66.78; H, 6.38; N, 13.49; Cl, 8.05.

Example 230

- 5 **4-[(2,3-Dihydro-1H-indol-1-yl)carbonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, monohydrochloride.**

Example 230 was prepared from N-chlorocarbonyl-indoline as
 10 described for Example 229, mp 156-166°C.

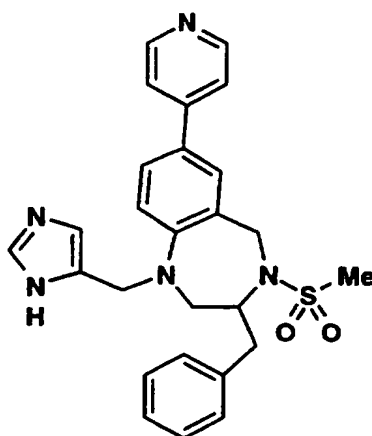
MS (M + H)⁺ 450

Analysis calculated for C₂₈H₂₇N₅O • 0.5 H₂O • 1.5 HCl.

Calc'd: C, 65.52; H, 5.79; N, 13.65; Cl, 10.36.

Found: C, 65.40; H, 5.74; N, 13.47; Cl, 10.49.

15

Example 231

- 20 **2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(phenylmethyl)-7-(4-pyridinyl)-1H-1,4-benzodiazepine, trihydrate.**

A. 2,3,4,5-Tetrahydro-1-(trifluoroacetyl)-4-(methylsulfonyl)-3-(phenylmethyl)-7-bromo-1H-1,4-benzodiazepine

Trifluoroacetic anhydride (1.2 mmol, 165 mL) was added to a solution of Compound A of Example 78 (0.3 mmol) and triethylamine (2.75 mmol, 384 mL) in CH₂Cl₂ (4 mL) and the homogeneous solution was maintained at rt for 5 hrs. The reaction was concentrated and purified by flash chromatography (40% EtOAc/Hex) to isolate Compound A as a fluffy white solid (100 mg, 68%). MS (M+NH₄) 508.

B. 2,3,4,5-Tetrahydro-1-(trifluoroacetyl)-4-(methylsulfonyl)-3-(phenylmethyl)-7-(4-pyridinyl)-1H-1,4-benzodiazepine

Compound A (0.15 mmol), 4-stannylpyridine (0.3 mmol, 110 mg) and 15 mol% Pd(PPh₃)₄ (26 mg) in 3 mL THF was degassed and heated to reflux under argon. Over the period of 48 hrs, an additional 20 mol% catalyst was added until starting material was fully consumed. The reaction was concentrated and purified by flash chromatography (EtOAc) to isolate Compound B as a yellow oil (46 mg, 63%). MS (M+H) 490.

C. 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(phenylmethyl)-7-(4-pyridinyl)-1H-1,4-benzodiazepine, trihydrochloride

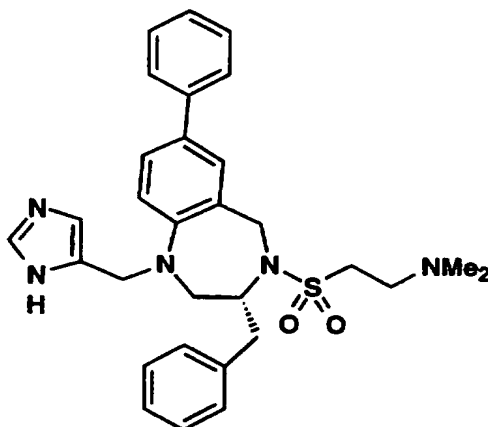
NaOH (5 drops of 2N NaOH aqueous solution) was added to a solution of Compound B (40 mg, 0.082 mmol) in 3 mL MeOH and the mixture was maintained at RT for 20 min and concentrated. The residue was partitioned between 2N NaOH (5 mL) and 10% isopropanol-CH₂Cl₂ (5 mL) and extracted with 10% isopropanol-CH₂Cl₂ (3X5 mL), dried over Na₂SO₄ and concentrated. This material was dissolved in 1 mL of 1:1 AcOH:dichloroethane and treated with 4-formylimidazole (0.66 mmol, 63 mg) and NaBH(OAc)₃ (0.66 mmol, 140 mg) and the mixture was heated at 50°C for 2 hrs and concentrated. The residue was partitioned between 2N NaOH-brine-sat. NH₄OH (10:10:0.3, 23 ml total) and 10% isopropanol-CH₂Cl₂ (5 mL) and the aqueous phase was extracted with 10% isopropanol-CH₂Cl₂ (2X5 mL). The combined organic phases were concentrated and purified with prep. HPLC (YMC S5 ODS 20 X100 mm, gradient elution with 15 to 75 % buffer B over 60 min. Buffer A = MeOH : H₂O:TFA (10:90:0.1); Buffer B = MeOH:H₂O:TFA (90:10:0.1); flow rate 25 ml/min). The TFA salt was

converted to HCl salt with 1N HCl to produce Examp^l 231 as a yellow solid (6.0 mg, 13%).

MS (M+H)⁺ 474

1H NMR (CD₃OD) δ 8.9 (s, 1H), 8.7 (m, 2H), 8.3 (m, 2H), 7.8 (m, 2H), 7.5 (s, 1H), 7.3 (m, 4H), 7.0 (d, J=9Hz, 1H), 4.8 (d, J=8Hz, 2H), 4.65 (t, J=14Hz, 2H), 4.45 (br s, 1H), 3.7 (dd, J=7,14 Hz, 1H), 3.4 (dd, J=7,5 Hz, 1H), 2.96 (dd, J=14,7 Hz, 1H), 2.8 (dd, J=14,7 Hz, 1H), 2.3 (s, 3H).

Example 232



(R)-4-[[2-(Dimethylamino)ethyl]sulfonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-3-(phenylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate (1:1).

A. (R)-7-Bromo-2,3,4,5-tetrahydro-3-(phenylmethyl)-1H-1,4-benzodiazepine

Compound A was prepared from Compound A of Example 224 as described for Compound B of Example 75.

B. (R)-7-Phenyl-2,3,4,5-tetrahydro-3-(phenylmethyl)-1H-1,4-benzodiazepine

To a mixture of Compound A (500 mg, 1.58 mmol) in toluene (20 mL) and aqueous sodium bicarbonate (10 mL, saturated solution) under argon was added a solution of phenylboronic acid (385 mg in 5 mL absolute ethanol). Tetrakis(triphenylphosphine) palladium(0) (91 mg) was added, and the solution heated to reflux (~80°C). After 18 hours, the mixture was cooled to room temperature and partitioned between aqueous sodium hydroxide (100 mL, 3N) and ethyl acetate (100 mL). The mixture was

xtracted with ethyl acetate (2 x 200 mL), and the organic layers were combined, dried (MgSO₄) and concentrated in vacuum to an oil, which was purified using flash chromatography (60 g silica, 10:0.5: 0.05 ethyl acetate : methanol : ammonium hydroxide) to provide Compound B (350 mg, 70 %) as a waxy solid

C. (R)-4-Ethenylsulfonyl-2,3,4,5-tetrahydro-7-phenyl-3-(phenylmethyl)-1H-1,4-benzodiazepine

To a mixture of Compound B (45 mg, 0.14 mmol) in methylene chloride (5 mL) and aqueous sodium hydroxide (1 mL, 1M solution) was added 2-chloroethane sulfonyl chloride (0.8 mL, 0.07 mmol). Additional portions of 2-chloroethane sulfonyl chloride (0.1 mL, 0.2 mL, 0.2 mL) were added over a period of 6 hours and the mixture was stirred for 18 hours, poured into brine and extracted with ethyl acetate (3 x 100 mL). The organic layers were combined, dried (MgSO₄) and concentrated in vacuum to an oil, which was purified using preparative HPLC (ODS column, aqueous methanol gradient containing trifluoroacetic acid). Appropriate product containing samples were pooled and concentrated under vacuum to provide Compound C (10 mg, 17 %) as a clear oil.

D. (R)-4-[[2-(Dimethylamino)ethyl]sulfonyl]-2,3,4,5-tetrahydro-7-phenyl-3-(phenylmethyl)-1H-1,4-benzodiazepine

To a solution of Compound C (20 mg, 0.025 mmol) in tetrahydrofuran (2 mL) was added a solution of dimethyl amine (1 mL, 2M in THF). The solution was heated in a sealed pressure bottle at 60°C for 18 hrs, cooled to room temperature and concentrated in vacuum to an oil.

E. (R)-4-[[2-(Dimethylamino)ethyl]sulfonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-3-(phenylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate (1:1)

A solution of Compound D (20 mg, crude, assume 0.05 mmol) and 4-formyl imidazole (10 mg, 0.1 mmol) in dichloroethane (4 mL) and acetic acid (2 mL) was stirred at room temperature for 30 min. Sodium triacetoxy borohydride (22 mg, 0.1 mmole) was added and the solution was stirred for 48 hour, diluted with ethyl acetate (20 mL) and ammonium hydroxide (5 mL, conc), and stirred for an additional 30 min. The mixture was extracted with ethyl acetate (2 x 25 mL), and the combined organic extracts were washed

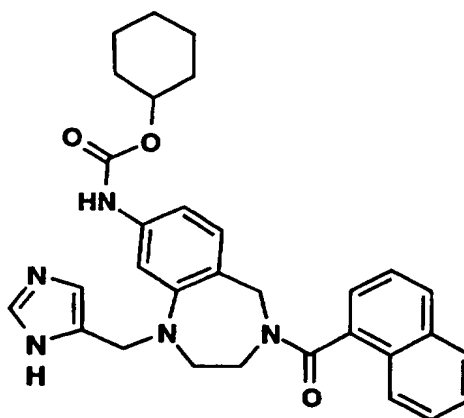
with aqueous sodium bicarbonate (25 ml, saturated solution), and then ammonium chloride (25 mL, sat aqueous solution), dried (Na₂SO₄), and concentrated in vacuo to a semi-solid. The crude product was purified by preparative HPLC (aqueous methanol gradient containing 0.1% trifluoroacetic acid, C-18 column) and lyophilized to provide Example 232 as a white solid (10 mg, 37 % yield from Compound C). mp 115-120 °C.

MS (M+H)⁺ 530

¹H NMR (200 MHz, CD₃OD) δ 8.8 (d, 1H), 7.7-7.4 (m, 12H), 7.1 (d, 1H), 4.9 (s, 6H), 3.4-3.1 (m, 8 H), 3.8-3.2 (m, 8H), 2.7 (s, 6H).

10

Example 233



[2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepin-8-yl]carbamic acid, cyclohexyl ester, dihydrochloride.

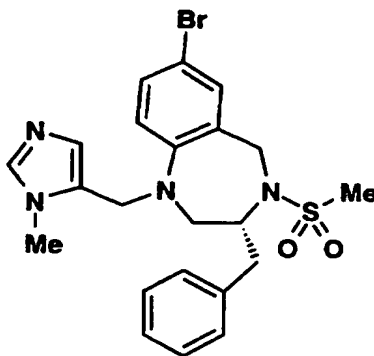
A solution of cyclohexanol (0.14 mL, 0.137 g, 1.38 mmol) and phosgene (0.14 mL, 2 M solution in THF) was stirred at 4°C for 2 hrs. To this cold solution were added triethylamine (0.19 mL, 0.14 g, 1.38 mmol) and Example 26 (0.050 g, 0.12 mmol). After stirring for 16 hrs at 4°C the mixture was diluted with chloroform and NaHCO₃ solution and the layers were separated. The aqueous layer was extracted with CHCl₃ (2x30 mL) and the combined organic layers were washed with brine (1x30 mL), dried over MgSO₄, filtered and concentrated. The residue was treated with MeOH and 1N NaOH for 30 min. The crude product was purified by preparative HPLC (aqueous methanol gradient containing 0.1% trifluoroacetic acid, C-18 column) and lyophilized. The residue was treated with HCl/ether to afford Example 233 (0.030 g, 46 %) as a light yellow solid.

MS (M + H)⁺ 524

¹H NMR (270 MHz, CD₃OD): δ 8.0-6.9 (m, 11H), 6.81 (d, 0.5H, J = 8 Hz), 5.85 (d, 0.5H, J = 9 Hz), 5.85 (m, 1H), 4.4-4.0 (m, 3H), 3.9-3.7 (m, 0.5H), 3.4-3.1 (m, 1.5H), 2.88 (m, 1H), 2.0-1.2 (m, 12 H).

5

Example 234



10 **(R)-7-Bromo-2,3,4,5-tetrahydro-1-(1-methyl-1H-imidazol-5-yl)methyl-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, hydrochloride.**

15 **A. (R)-7-Bromo-2,3,4,5-tetrahydro-1-((((1,1-dimethylethoxy)-carbonyl)-1H-imidazol-4-yl)methyl)-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine**

To a solution of 260 mg (0.55 mmol) of Example 224 in 10 ml of methylene chloride was added 131 mg (0.60 mmol) of BOC anhydride and 3 mg (0.025 mmol) of DMAP. The clear colorless solution was stirred at rt under argon for 3 hr. An additional 40 mg of BOC anhydride was added and stirring was continued overnight. The mixture, without workup, was placed a 30 cc column of silica gel and eluted with 25% ethyl acetate:hexane to afford 290 mg (0.55 mmol, 100%) of Compound A as a solid white foam.

25 **B. (R)-7-Bromo-2,3,4,5-tetrahydro-1-(1-methyl-1H-imidazol-5-yl)methyl-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, hydrochloride.**

To a solution of 275 mg (0.48 mmol) of Compound A and 0.091 ml (0.52 mmol) of DIEA in 5 ml of methylene chloride, at -78°C and under argon, was added dropwise 0.059 ml (0.52 mmol) of methyl triflate. The mixture was allowed to warm to rt over 3 hr. An additional 0.091 ml (0.52

mmol) of DIEA and 0.059 ml (0.52 mmol) of methyl triflate were added. Stirring was continued at rt overnight. Three more additions of 0.091 ml (0.52 mmol) of diisopropylethylamine and 0.059 ml (0.52 mmol) of methyl triflate were made at 1 hr intervals. The reaction, without workup, was placed a 50 cc column of silica gel. Elution with CHCl₃:MeOH (98:2) afforded 134 mg of the free base of Example 234 as a white foam. To this material, as a solution in 2 ml of ethyl acetate, was added dropwise 0.26 ml of 1N HCl/ether. The resulting solid was filtered to give Example 234 (102 mg, 38%) as a white solid.

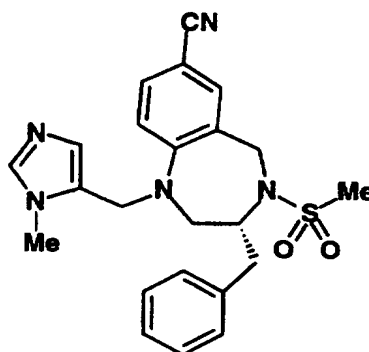
MS (M + H)⁺ 489, 491

Analysis calculated for C₂₂H₂₄N₄O₂Cl • 0.25 EtOAc • 1.25 HCl.

Calc'd: C, 49.59; H, 5.11; N, 10.06.

Found: C, 49.97; H, 5.15; N, 9.90.

Example 235

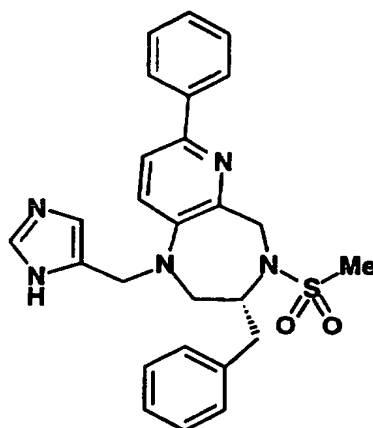


(R)-7-Cyano-2,3,4,5-tetrahydro-1-[(1-methyl-1H-imidazol-5-yl)methyl]-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.

To a solution of 200 mg (0.38 mmol) of (R)-7-cyano-2,3,4,5-tetrahydro-1-[(1,1-dimethylethoxy)-carbonyl]-1H-imidazol-4-yl)methyl]-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine (prepared from Example 224 as described for Compound A of Example 225) in 2 mL of methylene chloride, at -78°C and under argon, was added dropwise 59 µL (0.48 mmol) of methyl triflate. The reaction was allowed to warm to rt, during which time a white precipitate was obtained. Stirring was continued at rt for 3 hr, after which time 140 µL (0.8 mmol) of DIEA was added and stirring continued overnight at rt. The mixture, without workup, was subjected to

flash chromatography on a 30 cc column of silica gel. Elution with 2% MeOH-CHCl₃ afforded 122 mg (0.28 mmol, 74 %) of a clear colorless oil which crystallized on standing. This material was converted to its hydrochloride by the addition of 0.28 mL of 1M HCl in ether to a methylen
5 chloride solution (2 mL) of the free base. A white precipitate was obtained which on filtration afforded 90 mg of Example 235 as a white powder.
MS (M+H)⁺ 436

Example 236



(R)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-7-phenyl-3-(phenylmethyl)-1H-pyrido[3,2-e]-1,4-diazepine, monohydrochloride. BMS-214693

A. 2-Hydroxy-5-nitro-6-methylpyridine

To a suspension of a 2:1 mixture of 2-amino-5-nitro-6-methylpyridine and 2-amino-3-nitro-6-methylpyridine (2.5 g, 16.3 mmol) in 15 mL of water at 0°C was added concentrated sulfuric acid (5 mL), followed
20 by a solution of NaNO₂ (2.25 g, 32.6 mmol) in 5 mL of water dropwise over 90 minutes. The solution was stirred 5 hours as it warmed to room temperature, cooled to 0°C and filtered. The solid was washed with water (2x) and dried under vacuum to afford 1.84 g of a >4:1 mixture (by HPLC) of Compound A and 2-hydroxy-3-nitro-6-methylpyridine (73%) as a tan solid.

B. 2-Chloro-5-nitro-6-methylpyridin

A mixture of Compound A, 2-hydroxy-3-nitro-6-methylpyridine (0.93 g, 6.05 mmol) and phosphorus pentachloride (48.9 g, 235 mmol) in toluene (10 mL) was heated at 92°C for 16 hours and cooled to 0°C. Ice was added and the mixture was stirred and partitioned. The aqueous layer was washed with toluene and the combined organic phases were dried (magnesium sulfate), filtered and evaporated to afford 1.03 g of a 6:1 mixture of Compound B and 2-chloro-3-nitro-6-methylpyridine (100%) as a reddish brown crystalline semi-solid.

C. 2-Phenyl-5-nitro-6-methylpyridine

A mixture of Compound B and 2-chloro-3-nitro-6-methylpyridine (0.42 g, 2.40 mmol) in THF (10 mL) was degassed with nitrogen. Tetrakis(triphenylphosphine) palladium (28 mg, 0.024 mmol) was added and the mixture was stirred 30 minutes. Phenylboronic acid (0.44g, 3.6 mmol) and 2M Na₂CO₃ (1.8 mL) were added and the mixture was heated at 75°C for 17 hours and stirred at room temperature for 48 hours. Methylene chloride was added and the mixture was filtered through celite and partitioned. The mixture was washed with saturated aqueous NaHCO₃, dried (magnesium sulfate), filtered and evaporated to afford 0.77 g of brown solid. Flash chromatography (silica, 10% ethyl acetate/hexanes) afforded 0.37 g of Compound C (72%) as an off white solid and 0.05 g of 2-phenyl-3-nitro-6-methylpyridine (10%) as an oil.

D. 2-Phenyl-5-amino-6-methylpyridine

To a suspension of Compound C (3.0 g, 14 mmol) in concentrated HCl (30 mL) was added tin chloride dihydrate (9.91 g, 44 mmol) in portions over 45 minutes. The solution was allowed to warm to room temperature over 2 hours, heated at 78°C for 15 minutes, cooled to 0°C, neutralized with 4M NaOH and extracted with methylene chloride (3x). The combined organic phases were dried (magnesium sulfate), filtered and evaporated to afford 2.62 g of Compound D (100%) as a yellow oil which crystallized on standing.

E. 2-Phenyl-5-(phenylsulfonylamino)-6-methylpyridine

A mixture of 2-phenyl-5-amino-6-methylpyridine (2.29 g, 12.4 mmol) and benzenesulfonyl chloride (1.65 mL, 12.9 mmol) was heated at

88°C for 15 hours. The mixture was cooled and the resulting glass was dissolved in methylene chloride/10% NaOH. The mixture was partitioned, the organic phase was washed with 10% NaOH and the combined aqueous phases were acidified with concentrated HCl and extracted with methylene chloride (2x). The combined organic phases were dried (magnesium sulfate), filtered and evaporated to afford 3.40 g of Compound D (85%) as a light yellow crystalline solid.

F. 2-Phenyl-5-(phenylsulfonylamino)-6-methylpyridine-N-oxide

To a suspension of Compound E (3.0 g, 9.24 mmol) in acetic acid (28 mL) was added 30% aqueous hydrogen peroxide (9.25 mL). The mixture was heated at 72°C for 4 hours and at 62°C for 22 hours. An additional 3 mL of H₂O₂ was added and the mixture was heated at 54°C for 20 hours and poured onto ice. The mixture was allowed to stand overnight, 200 mL of water was added and the resulting solid was filtered, washed with water and ether and dried under vacuum to afford 1.43 g (46%) of Compound F as a yellow solid contaminated with Compound E. The combined water and ether washes were extracted with methylene chloride to afford 1.0 g of an approximate 4:1 mixture of Compound E and Compound F. MS (M+H)⁺ 341.1.

G. 2-Phenyl-5-(phenylsulfonylamino)-6-acetoxymethylpyridine

A solution of crude Compound F (0.50 g, <1.47 mmol) and acetic anhydride (2.5 mL) in acetic acid (5 mL) was heated at 90°C for 4 hours, cooled, and poured onto ice. After standing overnight, the mixture was extracted twice with methylene chloride and the combined organic extracts were dried (MgSO₄), filtered and evaporated to afford Compound G (0.60 g, >100%) as a yellow foamy gum.

H. 2-Phenyl-5-(phenylsulfonylamino)-6-hydroxymethylpyridine

A mixture of Compound G (0.60 g, <1.47 mmol) in 2M NaOH (2 mL) was heated at 50°C for 2.25 hours and cooled to 0°C. Methylene chloride was added, followed by concentrated aqueous HCl until the solid dissolved. Solid Na₂HPO₄ was added until the aqueous phase was pH 7, and the

mixture was partitioned. The aqueous phase was extracted with methylene chloride and the combined organic extracts were dried (MgSO₄), filtered and evaporated. The residue was flash chromatographed on silica with 50% ethyl acetate/hexanes to afford 0.09 g of Compound F and 0.24 g of
5 Compound H (48% from crude compound F) as a gum.

I. 2-Phenyl-5-(phenylsulfonylamino)-pyridine-6-carboxaldehyde

To a solution of crude Compound H (0.70 g, 2.06 mmol) in THF (10
10 mL) was added MnO₂ (0.36 g, 4.11 mmol). The mixture was stirred at room temperature and additional MnO₂ was added at the following times: 1 hour, 0.36 g; 2 hour, 0.36 g; 3 hour, 0.36 g; 7.5 hour, 0.72 g; 22.5 hour, 0.72 g; 32 hour, 0.72 g. After stirring for 32.5 hours, the mixture was filtered through celite, the pad was washed three times with celite and the filtrate was
15 evaporated to afford 0.55 g of Compound I (79%) as an orange solid. MS (M+H)⁺ 339.0.

J. D-[N-(2-phenyl-5-(phenylsulfonylamino)-6-pyridinylmethyl)-phenylalanine], methyl ester

A suspension of Compound I (0.55 g, 1.62 mmol), D-phenylalanine methyl ester hydrochloride (1.05 g, 4.88 mmol), NaOAc (0.40 g, 4.88 mmol) and 10% Pd/C (50 mg) in 4 mL methanol/2 mL acetic acid was
20 hydrogenated with a balloon for 18 hours and filtered through celite. The pad was rinsed twice with methanol and the filtrate was evaporated. The residue was partitioned between pH 7 phosphate buffer and methylene
25 chloride. The aqueous phase was extracted with methylene chloride and the combined organic extracts were dried (MgSO₄), filtered and evaporated to afford Compound J (1.21 g, >100%).

K. (R)-2,3,4,5-Tetrahydro-7-phenyl-3-(phenylmethyl)-1H-pyrido[3,2-e]-1,4-diazepin-2-one

A mixture of Compound J (1.21 g, < 1.62 mmol) and polyphosphoric acid (16 g) was heated at 100°C for 5 hours. Ice and methylene chloride were added and the mixture was chilled, made basic
35 with 4N NaOH and partitioned. The aqueous phase was washed twice with methylene chloride and the combined organic extracts were dried (MgSO₄), filtered and evaporated. The residue was flash chromatographed on silica

with 75% ethyl acetate/hexanes to afford 0.31 g (58% from Compound I) of Compound K as an off white solid. MS (M+H)+ 330.0.

L. (R)-2,3,4,5-Tetrahydro-4-(methylsulfonyl)-7-phenyl-3-(phenylmethyl)-1H-pyrido[3,2-e]-1,4-diazepin-2-one

To a solution of Compound K (117 mg, 0.36 mmol) and TEA (0.06 mL, 0.43 mmol) in methylene chloride (3 mL) at 0°C was added mesyl chloride (0.033 mL, 0.43 mmol). The solution was stirred at 0°C for 30 minutes and at room temperature for 90 minutes. Additional TEA (0.06 mL) and mesyl chloride (0.032 mL) were added and the solution was stirred for 1 hour and partitioned between aqueous NaHCO₃ and methylene chloride containing a little isopropanol (<10%). The aqueous layer was washed with methylene chloride and the combined organic extracts were dried (MgSO₄), filtered and evaporated to afford 145 mg of Compound L as a solid (100%). MS (M+H)+ 408.1.

M. (R)-2,3,4,5-Tetrahydro-4-(methylsulfonyl)-7-phenyl-3-(phenylmethyl)-1H-pyrido[3,2-e]-1,4-diazepine

To a solution of Compound L (53 mg, 0.13 mmol) in THF (2 mL) at 0°C was added 1 M borane in THF (0.39 mL). The solution was allowed to warm to room temperature overnight, methanol was added and the mixture was evaporated. The residue was dissolved in a small amount of 10% HCl and methanol, warmed until a clear solution was obtained, and the methanol was evaporated. Methylene chloride was added followed by solid K₂CO₃ until the aqueous layer was pH 11. The mixture was partitioned and the aqueous layer was washed with methylene chloride and the combined organic extracts were dried (MgSO₄), filtered and evaporated. The residue was subjected to preparative TLC on silica with 50% ethyl acetate/hexanes. The main mid R_f band was cut and extracted with methylene chloride containing a few drops of methanol to afford 25 mg of Compound M as a light yellow foam (49%).

N. (R)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-7-phenyl-3-(phenylmethyl)-1H-pyrido[3,2-e]-1,4-diazepine, monohydrochloride.

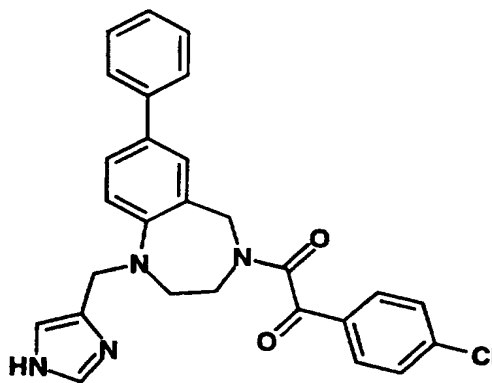
To a solution of Compound M (24 mg, 0.06 mmol) and imidazol-4-carboxaldehyde (17 mg, 0.18 mmol) in dichloroethane (1 mL)/ acetic acid

(0.5 mL) was added sodium triacetoxyborohydride (32 mg, 0.15 mmol). The solution was stirred 1 hour and additional aldehyde (16 mg) and hydride (16 mg) were added. The solution was stirred 45 minutes and additional hydride (16 mg) was added. NH₄OH (0.5 mL) was added, followed by ethyl acetate and aqueous NaHCO₃. The mixture was partitioned and the aqueous layer was washed with ethyl acetate and the combined organic extracts were washed with saturated NaHCO₃ and brine, dried (MgSO₄), filtered and evaporated to afford the free base of Compound N (25 mg, 89%) as a white foamy gum. This material was dissolved in methylene chloride and the solution filtered through glass wool and evaporated. The residue was dissolved in methanol, 0.5 mL of 1M HCl in ether was added and the mixture was evaporated. The residue was evaporated from methanol, dissolved in 2 mL of methanol and the solution filtered through glass wool. The filtrate was evaporated and the residue dissolved in 0.5 mL of methanol. Ether (10 mL) was added and the resulting precipitate was filtered, rinsed with ether and dried to afford Example 236 (24 mg) as a yellow solid.

MS (M+H)⁺ 474.3.

¹H (CD₃OD) δ 2.18, 3H, s; 2.76-2.92, 2H, m; 3.65, 1H, dd (J = 4.7, 15.2 Hz); 3.98, 1H, dd (J = 10.6, 15.2 Hz); 4.75, 1H, m; 5.18, 1H, d (J = 18.8 Hz); 7.26-7.40, 5H, m; 7.58-7.61, 4H, m; 7.76-7.90 4H, m.

Example 237



4-[2-(4-Chlorophenyl)-1,2-dioxoethyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, hydrochlorid .

A solution of HOAt (0.013 gm, 0.092 mmol) in DMF (0.5 mL) was added to 2-(4-chlorophenyl)-2-oxo-acetic acid (0.017 g, 0.092 mmol).

Solutions in DMF of Compound B of Example 33 (0.2 M, 0.46 mL, 0.092 mmol) and DIC (0.2 M, 0.014 mL, 0.092 mmol) were added to the mixture, which was stirred at room temperature for 16h. The mixture was purified by ion exchange chromatography on a solid phase extraction cartridge using the following protocol:

- 1) Conditioned a Varian solid phase extraction column (1.5 g, SCX cation exchange) with 10 mL of MeOH/CH₂Cl₂
- 2) Loaded mixture onto column using a 10 mL syringe to pressurize the system
- 3) Wash column with 3 X 7.5 mL MeOH/CH₂Cl₂ (1:1)
- 4) Wash the column with 1 X 7.5 mL of 0.01 N ammonia in MeOH
- 5) Eluted column with 7.5 mL of 1.0 N ammonia in MeOH and collect into a tared receiving tube.

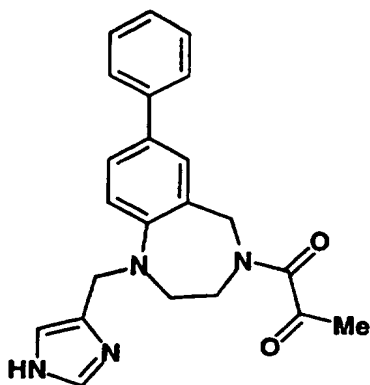
The product was concentrated on a Savant Speed Vac (approx. 2mm Hg for 20 hr). The residue was dissolved in CH₃CN (2 mL), 1N HCl (0.10 mL) and water (1 mL) and lyophilized to afford Example 237 (0.042 gm, 86%) as a white lyophilate.

MS: (M+H)⁺ 471

Analysis calculated for C₂₇H₂₃N₄O₂Cl • 0.15 CH₃CN • 1.0 HCl • 0.84 H₂O.

Calc'd: C, 61.40; H, 4.93; N, 10.88.

Found: C, 61.41; H, 5.02; N, 11.28.

Example 238

- 5 **4-(1,2-Dioxopropyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, hydrochloride.**

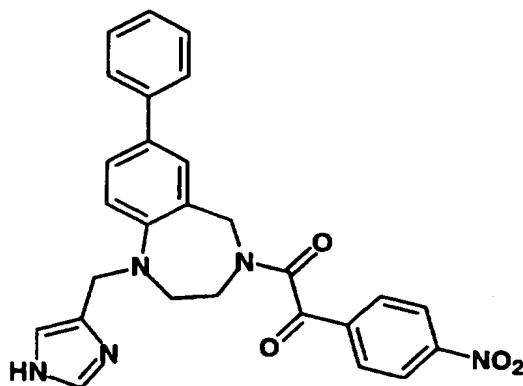
Example 238 was prepared from pyruvic acid as described for Example 237.

10 MS: (M+H)⁺ 375

Analysis calculated for C₂₂H₂₂N₄O₂ • 1.0 HCl • 0.67 H₂O.

Calc'd: C, 62.47; H, 5.80; N, 13.25.

Found: C, 62.46; H, 5.59; N, 13.28.

Example 239

5 **2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[2-(4-nitrophenyl)-1,2-dioxoethyl]-7-phenyl-1H-1,4-benzodiazepine, hydrochloride.**

Example 239 was prepared from 4-nitrophenylpyruvic acid as described for Example 237.

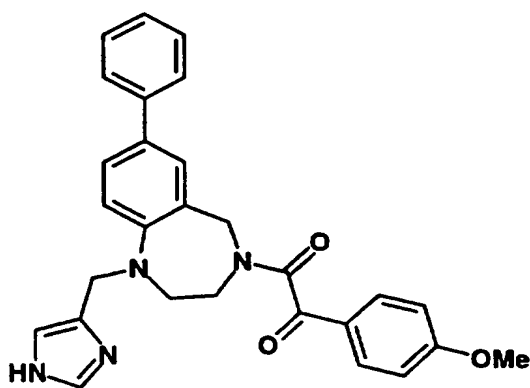
10 MS: (M+H)⁺ 482

Analysis calculated for C₂₇H₂₃N₅O₄ • 1.0 HCl • 0.38 H₂O.

Calc'd: C, 61.79; H, 4.76; N, 13.34.

Found: C, 61.80; H, 4.72; N, 13.54.

15

Example 240

20 **2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[2-(4-methoxyphenyl)-1,2-dioxoethyl]-7-phenyl-1H-1,4-benzodiazepine, hydrochloride.**

Example 240 was prepared from 4-methoxyphenylpyruvic acid as described for Example 237.

MS: (M+H)⁺ 467

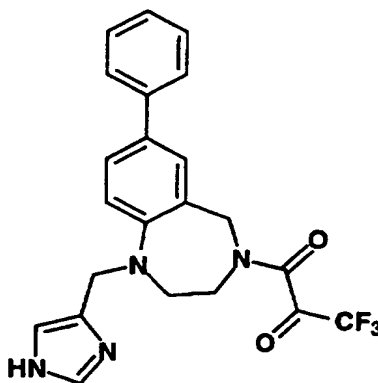
5 Analysis calculated for C₂₈H₂₆N₄O₃ • 1.0 HCl • 0.79 H₂O.

Calc'd: C, 65.02; H, 5.57; N, 10.83.

Found: C, 65.01; H, 5.66; N, 10.75.

Example 241

10



2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-(3,3,3-trifluoro-1,2-dioxopropyl)-1H-1,4-benzodiazepine, trifluoroacetate (1:2).

15

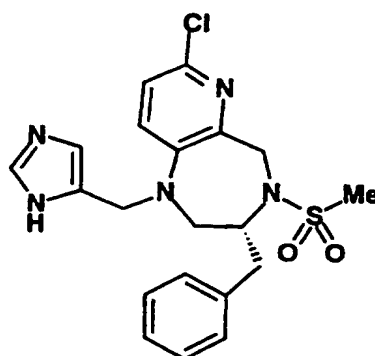
Example 241 was prepared from trifluoropyruvic acid as described for Example 237, with methylene chloride as cosolvent. Purification was by reverse phase preparative HPLC (aqueous methanol, 0.1% TFA).

MS: (M+H)⁺ 429

20 Analysis calculated for C₂₂H₁₉N₄O₂F₃ • 1.5 TFA • 0.81 H₂O.

Calc'd: C, 48.90; H, 3.63; N, 9.12.

Found: C, 48.90; H, 3.58; N, 9.13.

Example 242

(R)-7-Chloro-2,3,4,5-tetrahydro-1-[(1H-imidazol-4-yl)-methyl]-4-(methylsulfonyl)-3-(phenylmethyl)-1H-pyrido[3,2-e]-1,4-diazepine, hydrochloride.

A. 2-Chloro-5-(phenylsulfonylamino)-6-methylpyridine

Compound A was prepared from Compound B of Example 236 as described for Compound D of Example 236 and Compound E of Example 236.

B. 2-Chloro-5-(phenylsulfonylamino)-6-methylpyridine-N-oxide

To a suspension of Compound A (3.0 g, 10.6 mmol) in TFA (12.5 mL) was added 30% aqueous hydrogen peroxide (2.2 mL). The mixture was heated at reflux for 80 minutes. An additional 2.5 mL of H₂O₂ was added and the mixture was heated at reflux for 95 minutes. An additional 2.5 mL of H₂O₂ was added and the mixture was heated at reflux for 1 hour and poured onto ice. The mixture was allowed to stand overnight and was filtered. The solid was washed with water and dissolved in 10% isopropanol/methylene chloride and the solution dried to afford 2.44 g of Compound B contaminated with Compound A. An additional 0.33 g of impure compound B later precipitated from the aqueous filtrate for a combined yield of 2.77 g (88%). (M+H)⁺ 298.9.

C. 2-Chloro-5-(phenylsulfonylamino)-6-hydroxymethylpyridine

Compound C was prepared as a gum from Compound B as described for Compounds G and H of Example 236. (M+H)⁺ 299.0.

D. 2-Chloro-5-(phenylsulfonylamino)-pyridine-6-carboxaldehyde

To a solution of crude Compound C (2.45 g, 8.20 mmol) in THF (20 mL) was added MnO₂ (1.43 g, 16.4 mmol). The mixture was stirred at room temperature and additional MnO₂ was added at the following times: 1 hour, 2.86 g; 28 hour, 2.86 g. After stirring for 21 hours, the mixture was directly flash chromatographed (25% ethyl acetate/hexanes) to afford 0.82 g of crude compound D.

E. D-[N-(2-chloro-5-(phenylsulfonylamino)-6-pyridinylmethyl)-phenylalanine], methyl ester

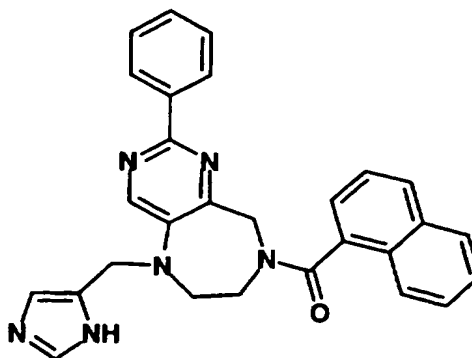
To a solution of crude Compound D (0.81 g, 2.73 mmol), D-phenylalanine methyl ester hydrochloride (0.88 g, 4.10 mmol) and NaOAc (0.67 g, 8.20 mmol) in 15 mL methylene chloride/3 mL acetic acid was added sodium triacetoxyborohydride (0.87 g, 4.10 mmol) in aliquots over 90 minutes. The mixture was stirred for 90 minutes and partitioned between pH 7 phosphate buffer and methylene chloride. The aqueous phase was extracted with methylene chloride and the combined organic extracts were dried (MgSO₄), filtered and evaporated to afford Compound E (1.62 g, >100%) as an orange gum.

F. (R)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-7-chloro-3-(phenylmethyl)-1H-pyrido[3,2-e]-1,4-diazepine, monohydrochloride

Example 242 was prepared from Compound E as described in the following sequence: Compound K of Example 236, Compound L of Example 236, Compound M of Example 236, Compound N of Example 236. The HCl salt was precipitated from isopropanol with ether to afford Example 242 as a very hygroscopic foam.

MS (M+H)⁺ 432.1.

¹³C (CDCl₃, free base) δ 37.96, 39.60, 47.97, 48.34, 55.73, 59.27, 118.66, 122.59, 124.89, 126.91, 128.64, 129.16, 135.59, 137.15, 138.88, 139.63, 144.10, 144.54, 182.64 ppm.

Example 243

6,7,8,9-Tetrahydro-5-(1H-imidazol-4-ylmethyl)-8-(1-naphthalenylcarbonyl)-2-phenyl-5H-pyrimido-[5,4-e][1,4]diazepine, monohydrochloride.

A. 2-Phenyl-5-bromo-4-pyrimidine carboxylic acid

To a solution of mucobromic acid (16 g, 62 mmol) in 800 ml of water was added benzamidinium hydrochloride hydrate (26 g, 166 mmol) and Triton B (100 ml, 40% in water). The solution was stirred 23 hours, filtered of a small amount of dark solid, and acidified with concentrated HCl. The gummy precipitate was filtered and recrystallized from 4:1 ethanol:water to afford 5.87 g (34%) of Compound A as a brown crystalline solid. Concentration of the mother liquor afforded an additional 1.72 g (44% total yield).

B. 2-Phenyl-5-(2-aminoethylamino)-4-pyrimidine carboxylic acid

A mixture of 3.0 g (10.8 mmol) of Compound A and 300 mg of copper sulfate in 15 ml each of water and ethylenediamine was heated at 100°C for 3 hr. The dark solution was evaporated to dryness and the semi-solid residue diluted with water to yield a voluminous white precipitate which was filtered, washed well with water, and air dried overnight to afford 2.45 g of Compound B as a light tan solid. The filtrate was evaporated to dryness and the residue diluted with water. Standing at rt afforded an additional 0.6 g of Compound B. The materials were combined and dried overnight at 60°C under vacuum to give 2.85 g (approx 100%) of Compound B as a pale yellow solid.

C. 6,7,8,9-Tetrahydro-2-phenyl-5H-pyrimido-[5,4-e][1,4]-diazepine

To a suspension of 2.8 g (10.8 mmol) of Compound B in 100 ml of pyridine was added 3.1 g (16.3 mmol) of EDC and 2.2 g (16.3 mmol) of HOBT and the slurry was stirred at rt, under argon, for 36 hr. The resulting hazy solution was evaporated to dryness and the semi-solid residue diluted with 10% i-propanol:water and washed with brine (2x). A bright yellow precipitate formed in the aqueous layer during the washing. Filtration of this material afforded 1.9 g of crude Compound C. This material was suspended into methanol and heated on the steam bath. The remaining insolubles were removed by filtration and the filter cake again extracted with hot methanol. The combined filtrates were evaporated to dryness to afford 1.53 g (59 %) of Compound C as a pale yellow powder.

D. 6,7,8,9-Tetrahydro-2-phenyl-5H-pyrimido-[5,4-e][1,4]-diazepine

To a stirred solution of 100 mg (0.42 mmol) of Compound C in 2 ml of glyme was added 85 mg (2.1 mmol) of lithium aluminum hydride and the reaction heated at reflux for 18 hr. To the reaction was added 0.5 ml of pyridine and an additional 80 mg of LAH and heating continued at 85°C for an additional 18 hr. The mixture was quenched by the addition of 5 ml of ethyl acetate, followed by 0.5 ml of conc NH₄OH. The resulting suspension was filtered and the filter cake washed well with ethyl acetate. The filtrate was evaporated to dryness and the resulting crude product used in the subsequent reaction without further purification. This material may also be flash chromatographed on silica with 10% methanol:ethyl acetate to afford pure Compound D as an orange crystalline solid.

E. 6,7,8,9-Tetrahydro-8-(1-naphthalenylcarbonyl)-2-phenyl-5H-pyrimido-[5,4-e][1,4]diazepine

To a solution of 80 mg (assumed 0.35 mmol) of crude Compound D in 3 ml of methylene chloride and 3 ml of 1N sodium hydroxide was added 60 µl (0.4 mmol) of 1-naphthoyl chloride. The reaction was stirred at 0°C for 1 hr. The organic layer was separated, washed with sat. ammonium chloride, dried (MgSO₄) and evaporated. The residue was subjected to

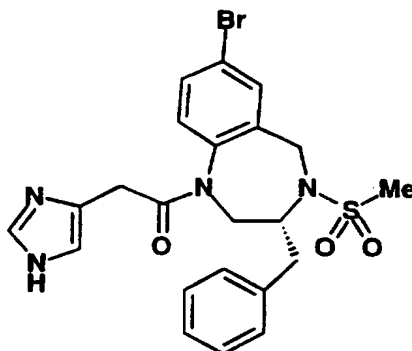
flash chromatography on silica gel. Elution with ethyl acetate-hexane (3:1) afforded 40 mg (25 % from Compound C) of Compound E as a foam.

F. 6,7,8,9-Tetrahydro-5-(1H-imidazol-4-ylmethyl)-8-(1-naphthalenylcarbonyl)-2-phenyl-5H-pyrimido-[5,4-e][1,4]diazepine, monohydrochloride

To a solution of 23 mg (0.062 mmol) of Compound E in 1 ml of methylene chloride and 0.2 ml of acetic acid was added 10 mg (1 mmol) of 4-formyl imidazole. The reaction was allowed to stir for 15 min and 21 mg (1 mmol) of sodium triacetoxyborohydride was added. Additional 10 mg portions of the imidazole and 21 mg portions of the hydride were added as above after 1,2,3 and 4 hr of stirring. Stirring was continued overnight. The reaction was diluted with methanol and, without further workup, subjected to preparative HPLC on a YMC ODS-A S10 column with gradient elution from 0-100% solvent B (A: 10% MeOH-H₂O + 0.1% TFA, B: 10% H₂O-MeOH + 0.1% TFA). The appropriate fractions were combined and evaporated. The residue was converted to the hydrochloride salt by dilution with methanolic HCl and removal of solvent to give 31 mg of yellow solid. This material was dissolved into minimal methanol and precipitated by the dropwise addition of ether to afford 12 mg (39%) of pure Example 243 as a yellow powder.

MS (M+H)⁺ 461.

¹H NMR (CD₃OD): δ 3.69 (2H, bs), 3.90 (2H, m), 4.20 (1H, m), 4.45 (1H, m), 4.70 (1H, m), 4.82 (1H, m), 5.49 (1H, m), 7.32-8.30 (11H, m), 8.43 (1H, s), 8.60 (1H, s), 8.95 (1H, m), 9.11 (1H, s).

Example 244

5 **(R)-7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylacetyl)-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.**

10 **A. (R)-7-Bromo-2,3,4,5-tetrahydro-4-(1,1-dimethylethoxycarbonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine**

To a solution of 250 mg (0.79 mmol) of Compound B of Example 224 in 5 ml of methylene chloride, at rt and under argon, was added 192 mg (0.88 mmol) of BOC anhydride as a solution in 1 ml of methylene chloride. After 1 hr, an additional 100 mg of BOC anhydride was added and stirring continued an additional 0.5 hr. The reaction, without workup, was subjected to flash chromatography on a 50 cc column of silica gel. Elution with 20% EtOAc-hexane afforded 319 mg (96 %) of Compound A as a white solid.

20 **B. (R)-7-Bromo-2,3,4,5-tetrahydro-1-(1-triphenylmethyl-imidazol-4-ylacetyl)-4-(1,1-dimethylethoxycarbonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine**

To a suspension of 2.2 g (6 mmol) of 1-triphenylmethyl-4-imidazolyl-acetic acid in 50 ml of THF, at rt and under argon, was added 836 μ l (6 mmol) of triethylamine. The resulting cloudy solution was cooled to -30°C and 839 μ l (6.6 mmoles) of *t*-butylchloroformate was added dropwise. After stirring an additional 0.5 hr at -30°C, a solution of 500 mg (1.2 mmoles) of Compound A in 10 ml of THF was added dropwise. The reaction was allowed to warm to rt over three hours and stirring was continued overnight. The resulting black reaction was diluted with ethyl acetate and washed with

brine (2x), dried (MgSO_4) and the solvent removed to yield a black foam residue which was subjected to flash chromatography on silica gel. Elution with 25% ethyl acetate-hexane afforded 376 mg (40 %) of Compound B as a gray solid foam, as well as 294 mg of Compound A.

5

C. (R)-7-Bromo-2,3,4,5-tetrahydro-1-(1-triphenylmethyl-imidazol-4-ylacetyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, hydrochloride

A solution of 370 mg (0.48 mmol) of Compound B in 2 ml of 1 M HCl in acetic acid was stirred at rt for 0.5 hr. The reaction was evaporated to dryness at low temperature and the residue diluted with ethyl acetate. Filtration of the resulting solid afforded 280 mg (83%) of Compound C.

10

15

D. (R)-7-Bromo-2,3,4,5-tetrahydro-1-(1-triphenylmethyl-imidazol-4-ylacetyl)-4-(methanesulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine

To a solution of 280 mg (0.4 mmol) of Compound C in 3 ml of methylene chloride, at rt and under argon, was added 167 μl (1.2 mmoles) of triethylamine, followed by 46 μl (0.6 mmole) of methanesulfonyl chloride. After stirring 0.5 hr, an additional 167 μl of triethylamine and 46 μl methanesulfonyl chloride was added and stirring continued for an additional 0.5 hr. The solution, without workup, was subjected to flash chromatography on a 50 cc column of silica gel. Elution with 50 % ethyl acetate-hexane afforded 165 mg (55%) of Compound D as a solid white foam.

20

25

E. (R)-7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylacetyl)-4-(methanesulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride

To a solution of 80 mg (0.11 mmol) of Compound D in 2 ml of methylene chloride was added 0.5 ml of triethylsilane and 1 ml of TFA and the solution stirred at rt, under argon, for 3 hr. The reaction was evaporated to dryness to yield a white solid residue which was diluted with ether and stirred 0.5 hr. The solvent was decanted and the remaining insolubles washed twice more with ether. The remaining solid was taken into ethyl acetate and washed with sat NaHCO_3 , brine, dried (MgSO_4) and the solvent removed to give 45 mg of solid white foam. This material was dissolved in minimal methylene chloride and 90 μl of 1M HCl in ether was added

30

35

dropwise. The reaction was diluted with additional ether and the resulting slurry allowed to stand overnight under refrigeration. The solid was filtered under an atmosphere of nitrogen to afford 36 mg (62 %) of Example 244 as a white powder.

5 MS (M+H)⁺ 503.

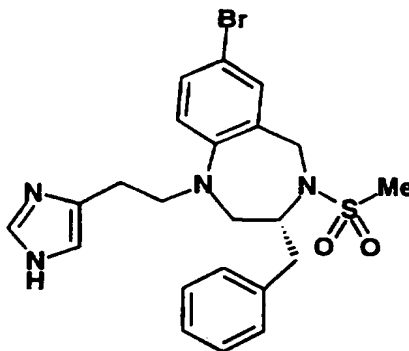
Analysis calculated for C₂₂H₂₃N₄O₃S • 1.5 HCl.

Calc'd: C, 47.35; H, 4.42; N, 10.04.

Found: C, 47.55; H, 4.41; N, 9.92.

10

Example 245



(R)-7-Bromo-2,3,4,5-tetrahydro-1-(2-1H-imidazol-4-ylethyl)-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.

15

To a solution of 80 mg (0.107 mmole) of the free base of Example 244 in 0.5 ml of THF, at rt and under argon, was added 1 ml of 1M borane in THF. The clear colorless solution was heated at reflux for 2 hr, 0.5 ml of conc. HCl was added and heating continued for an additional 2 hr at 65°C.

20

The reaction was diluted with water and washed twice with ethyl acetate. The combined organic layers were backwashed once with brine, dried and the solvent removed to afford a clear oil residue which was subjected to flash chromatography on a 30 cc column of silica gel. Elution with

25

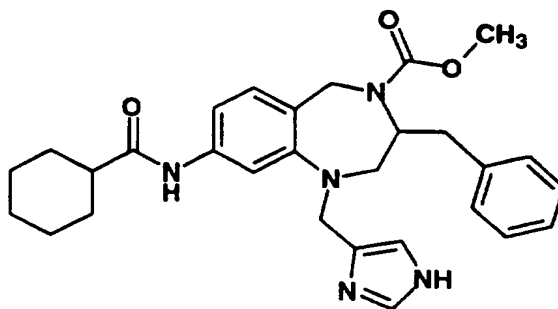
CHCl₃:MeOH:NH₄OH (95:5:0.5) afforded 112 mg of an oil. This material was diluted with 0.5 ml conc. HCl and again heated at 80°C for 2 hr. After cooling to rt, the reaction was diluted with water and extracted twice with ethyl acetate. The combined organic layers were dried (MgSO₄), and the solvent removed to give 30 mg of residue. Trituration of this material with ether afforded a white solid which was dissolved in 0.2 ml of methanol and

precipitated by the dropwise addition of ether. Filtration of the resulting solid afforded 12 mg (21 %) of Example 245 as a white powder.

MS (M+H)⁺ (high res): calc, 489.0957. Obs, 489.096.

¹³C NMR (67.8 MHz, CD₃OD): 24.7, 39.2, 40.3, 47.3, 53.3, 58.1, 60.8, 113.3, 118.1, 118.8, 128.3, 130.1, 130.8, 131.0, 132.4, 134.0, 135.3, 139.8, 149.9 ppm.

Example 246



8-[(Cyclohexylcarbonyl)amino]-1,2,3,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4H-1,4-benzodiazepine-4-carboxylic acid, methyl ester, dihydrochloride.

A. 8-Amino-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine-4-carboxylic acid, 1,1-dimethylethyl ester

Compound A was prepared as a white solid from Compound D of Example 98 as described for Example 26. The crude free base was carried on. MS (M+H)⁺ = 434.

B. 8-(Cyclohexylcarbonylamino)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine-4-carboxylic acid, 1,1-dimethylethyl ester

Compound B was prepared as a white foamy solid from Compound A as described for Example 27. The crude free base was carried on. MS (M+H)⁺ = 544.

C. N-[2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepin-8-yl]cyclohexanamide

Compound C was prepared as a light brown solid from Compound B by treatment with HCl/dioxane in methanol at rt. MS (M+H)⁺ = 444.

5

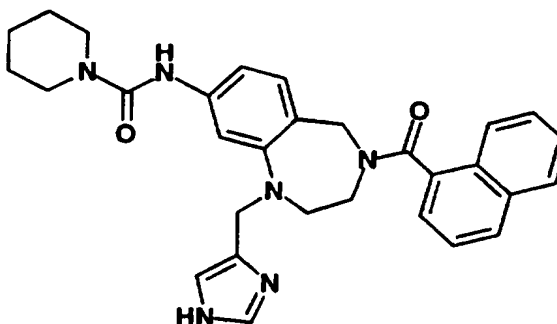
D. 8-[(Cyclohexylcarbonyl)amino]-1,2,3,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4H-1,4-benzodiazepine-4-carboxylic acid, methyl ester, dihydrochloride

Methyl chloroformate (0.05 g, 0.09 mmol) was added to a stirred solution of Compound C (0.05 g, 0.09 mmol) in CH₂Cl₂ at rt, under argon. After stirring for 3 days the mixture was partitioned with CHCl₃ (5 mL) and NaHCO₃ (2 mL). The aqueous layer was extracted with CHCl₃ (2 x 10 mL). The combined organic layers were washed with NaHCO₃ and brine, dried over MgSO₄, filtered and concentrated. The residue was purified by preparative HPLC, with a gradient of 50-100% aqueous methanol containing 0.1% TFA and the HCl salt was formed by treatment with 1M HCl/ether. MS (M+H)⁺ = 502.

¹H NMR (CD₃OD): δ 8.8 (s, 1H), 7.45-7.1 (m, 7.5 H), 7.05 (m, 1H), 6.8 (m, 0.5 H), 4.67-4.35 (m, 4H), 4.58 (s, 3H), 3.4-3.0 (m, 3 H), 2.9 (m, 1 H), 2.7 (m, 1H), 2.3 (m, 1H), 1.9-1.2 (m, 10 H).

20

Example 247



N-[2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepin-8-yl]-1-piperidin carboxamide, dihydrochloride .

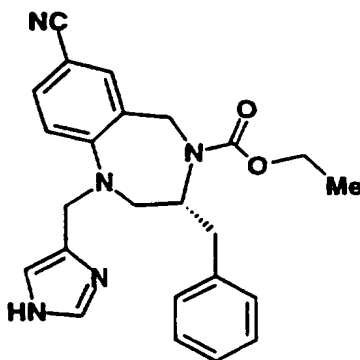
25

Carbonyldiimidazole (0.045 g, 0.137 mmol), was added to a solution of Example 26 (0.050 g, 0.125 mmol), and triethylamine (0.038 mL, 0.275 mmol) in dry methylene chloride (1 mL) at rt under argon. After stirring for 2 hr, piperidine (0.013 mL, 0.13 mmol) was added. After stirring for 15 hr, the reaction was diluted with NaHCO₃ and CHCl₃. The organic layer was washed with NaHCO₃, water, and brine (1x3 mL each), dried over MgSO₄, filtered and concentrated. The product was purified by reverse phase HPLC with a gradient of 40-90% aqueous methanol with 0.1 % TFA and the HCl salt was formed by treatment with 1M HCl/ether to afford Example 247 (0.006 g, 10 %).

MS (M+H)⁺ 509.

¹H NMR (CD₃OD): δ 8.5 (d, 1H, J = 19 Hz), 8.06-7.9 (m, 2H), 7.69-7.3 (m, 7H), 7.2 (d, 0.5H, J = 7 Hz), 6.9 (d, 0.5H, J = 7 Hz), 6.5 (d, 0.5 H, J = 7 Hz), 5.89 (t, 0.5 H), 4.6-3.88 (m, 4.5 H), 3.6-3.3 (m, 6H), 3.18-2.85 (m, 1.5H), 1.65 - 1.55 (m, 6H).

Example 248



(R)-7-Cyano-1,2,3,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4H-1,4-benzodiazepine-4-carboxylic acid, ethyl ester, hydrochloride.

A. (R)-7-Bromo-2,3,4,5-tetrahydro-3-(phenylmethyl)-1H-1,4-benzodiazepine-2,5-dione

To a stirred solution of 5-bromoisatoic anhydride (150g, 563 mmol) in anhydrous pyridine (1.5L) under argon was added D-phenylalanine methyl ester hydrochloride (127 g, 590 mmol) and 4-dimethylaminopyridine (2g). The resulting solution was refluxed for 3 days and cooled to room temperature. The solvent was evaporated. The residue was dissolved in CH_2Cl_2 (3 liter) and the solution was washed with 10% HCl and brine, dried over anhydrous Na_2SO_4 and evaporated to give a foam which was suspended in Et_2O (1.0L). The mixture was stirred and CH_2Cl_2 (100 ml) was added to help break up the emulsion. After cooling 3 hr in an ice bath, the solid was filtered, washed with Et_2O and a small amount of CH_2Cl_2 and dried in high vacuum to give 152g (78.4%) of Compound A.

^{13}C -NMR ($\text{DMSO}-d_6$) 33.31, 53.69, 115.94, 123.31, 126.43, 128.22, 129.39, 132.63, 134.97, 136.19, 137.76, 166.45, 171.11 ppm

B. (R)-7-Bromo-2,3,4,5-tetrahydro-3-(phenylmethyl)-1H-1,4-benzodiazepine

To a stirred and chilled (0° , ice bath) solution of Compound A (100 g, 290 mmol) in anhydrous THF (1.5L) under argon was added borane tetrahydrofuran complex (1.0M solution, 1450 ml, 1450 mmol). The resulting solution was gently refluxed overnight. The solution was cooled to 0° and MeOH was slowly added until foaming ceased. The solvent was evaporated to dryness. The residue was diluted with MeOH (900 ml), an aqueous solution of 25% HCl (180 ml) added and the mixture was gently refluxed under argon for 2 hr. The resulting solution was cooled to 0° in an ice bath, Et_2O (300ml) was slowly added and the mixture was stirred for 1 hr. The solid was filtered. The filtrate was evaporated and the residue and the solid were combined, rinsed with Et_2O (500 ml) and acetone (500 ml) and suspended in CH_2Cl_2 (2L) and water (1L). The pH of the slurry was adjusted to 11 with 3N NaOH. The CH_2Cl_2 layer was separated. The aqueous layer was saturated with NaCl and extracted with CH_2Cl_2 . The combined CH_2Cl_2 extracts were washed with brine, dried over anhydrous Na_2SO_4 and evaporated to give 89 g (97% yield) of Compound B as light tan solid.

¹³C-NMR (CDCl₃) 40.55, 52.19, 54.22, 61.74, 112.52, 120.25, 126.50, 128.60, 129.30, 130.13, 132.09, 133.96, 138.52, 148.13 ppm

5 **C. (R)-2,3,4,5-Tetrahydro-3-(phenylmethyl)-1H-1,4-benzodiazepine-7-carbonitrile**

To a stirred suspension of Compound B (60 g, 190 mmol) in anhydrous 1-methyl-2-pyrrolidinone (600 ml) under nitrogen was added copper(I) cyanide (51g, 569 mmol). The mixture was heated to 200° for 3.5hr. The mixture was slowly added to 15% ethylenediamine solution in
10 water (1.5 L) with vigorous stirring. After 1.0 hr stirring, the slurry was extracted with EtOAc (3x750ml). The EtOAc extracts were combined, washed with 10% NH₄OH (2x750ml) and brine, dried over anhydrous Na₂SO₄ and evaporated to give a black gum. This was passed through a pad of silica gel (E. Merck 230-400 mash, 1.2 kg) eluting with EtOAc to give
15 40 g (80%) of Compound C as a tan solid.

¹³C-NMR (CD₃OD) 40.84, 49.23, 51.62, 51.71, 62.56, 101.42, 119.14, 120.99, 127.56, 129.66, 130.38, 132.71, 134.86, 139.82, 156.29 ppm

20 **D. (R)-7-Cyano-1,2,3,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4H-1,4-benzodiazepine**

Compound D was prepared from Compound C by the following sequence: Compound C of Example 98, run in the absence of triethylamine and with purification by flash chromatography on silica with 4:1 hexanes:ethyl acetate; Compound D of Example 1; treatment with 4M HCl in
25 1:1 dioxane:ethyl acetate. MS (M+H)⁺ 344.

E. (R)-7-Cyano-1,2,3,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4H-1,4-benzodiazepine-4-carboxylic acid, ethyl ester, hydrochloride.

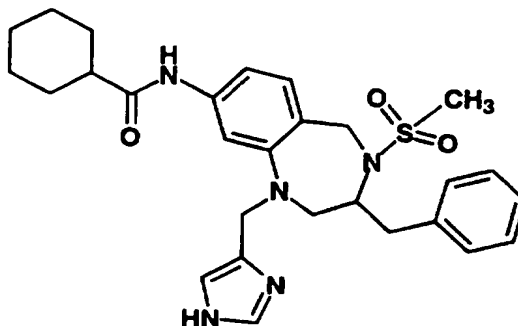
30 Ethylchloroformate (0.023 mL, 0.24 mmol) was added to a solution of Compound D (0.10 g, 0.22 mmol) and DIPEA (0.16 mL, 0.9 mmol) in dry methylene chloride (1 mL) at 0°C under argon. After stirring for 2.5 days the reaction was partitioned with NaHCO₃ (5 mL) and CHCl₃ (20 mL). The

aqueous layer was extracted with CHCl_3 (2 x 10 mL). The combined organic layers were washed with NaHCO_3 , water and brine, dried over MgSO_4 , filtered and concentrated. The product was purified on a flash column eluting with EtOAc (200 mL) and 19/1 $\text{CHCl}_3/\text{CH}_3\text{OH}$ (200 mL), treated with 1N NaOH to remove acylation on imidazole, and treated with HCl/ether to afford Example 248 (0.047 g, 52 %).

MS $(\text{M}+\text{H})^+ = 416$.

^1H NMR (CD_3OD): d 8.9 (d, 1H, $J = 16$ Hz), 7.48-7.12 (m, 8H), 6.9 (m, 1H), 5.0-4.4 (m, 5H), 4.8-3.7 (m, 3H), 3.4-3.2 (m, 2H), 2.89-2.7 (m, 2H), 1.03 (m, 3H).

Example 249



N-[2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methanesulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepin-8-yl]cyclohexanecarboxamide, dihydrochloride.

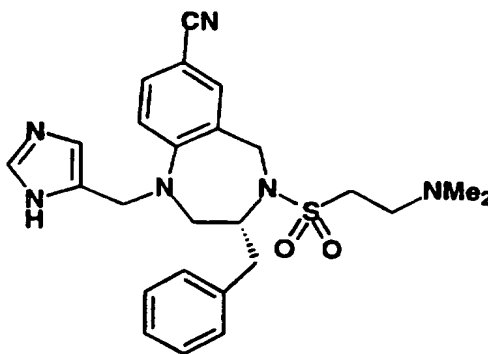
Methanesulphonyl chloride (0.024 mL, 0.38 mmol) was added to a heterogeneous mixture of Compound C of Example 246 (0.030 g, 0.054 mmol), DMF (0.2 mL), and triethylamine (0.2 mL) in dry methylene chloride (0.3 mL) at rt under argon. After stirring for 2.5 days another eq of mesylchloride was added. After stirring for 3 hr the mixture was diluted with NaHCO_3 and CHCl_3 , the layers were separated and the aqueous layer was extracted with chloroform (2 x 20 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried over MgSO_4 , filtered and concentrated. The residue was purified on a silica flash column eluting with

CHCl₃, and 9/1 CHCl₃/CH₃OH (200 mL each), to afford Example 249 (5 mg, 17 %).

MS (M+H)⁺ = 522.

¹H NMR (CD₃OD): δ 8.88 (s, 1H), 7.5 (m, 2H), 7.3 (m, 5H), 7.05 (d, 1H, J = 8 Hz), 6.8 (d, 1H, J = 8Hz), 4.8-4.2 (m, 5H), 3.6 (m, 1H), 3.2 (m, 1H), 3.0 (m, 1H), 2.7 (m, 1H), 2.3 (m, 3H), 1.6-1.9 (m, 5H), 1.1-1.5 (m, 4H), 0.9 (m, 2H).

Example 250



(R)-7-Cyano-4-[[2-(dimethylamino)ethyl]sulfonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4H-1,4-benzodiazepine, dihydrochloride.

A. (R)-7-Cyano-4-(ethenylsulfonyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4H-1,4-benzodiazepine

2-Chloroethanesulfonyl chloride (1.85 g, 11.4 mmol) was added to a solution of Compound D of Example 248 (1.0 g, 3.79 mmol) and DIPEA (2.6 mL, 15.2 mmol) in dichloromethane (16 mL) at 0°C under argon. After stirring for 16 hr, the reaction was diluted with chloroform and aq NaHCO₃. The layers were separated, the aqueous layer was reextracted twice with chloroform. The combined organic extract was washed twice with NaHCO₃ and brine, dried over MgSO₄, filtered and concentrated. The product was purified on a silica flash column eluting with 75% followed by 50% hexanes/ethyl acetate to afford Compound A (0.31 g, 23 %). MS: (M+H)⁺ = 434.

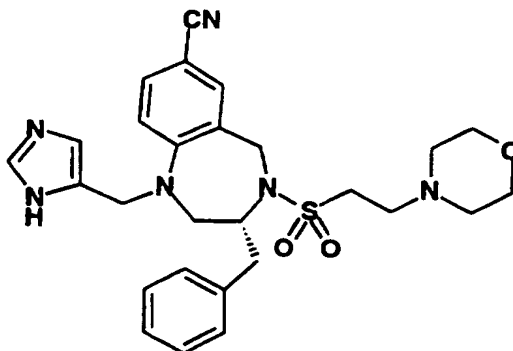
B. (R)-7-Cyano-4-[[2-(dimethylamino)ethyl]sulfonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4H-1,4-benzodiazepine, dihydrochloride

Compound A (0.59 g, 1.36 mmol) in a 2M solution of dimethylamine in THF (15 mL, 30 mmol) was warmed in a sealed tube to 60°C for 16 hours. The reaction was concentrated and the residue was purified by preparative HPLC (gradient of 30-90% aqueous methanol with 0.1 % TFA). The purified TFA salt was converted to its HCl salt with HCl/ether and lyophilized to afford Example 250 (11 mg, 1.7%).

MS: (M+H)⁺ = 479.

¹H NMR (CD₃OD): δ 8.9 (s, 1H), 7.5-7.2 (m, 8H), 6.9 (m, 1H), 4.8-4.4 (m, 5H), 3.95 (m, 1H), 3.4-3.1 (m, 5H), 3.0-2.7 (m, 8H).

Example 251

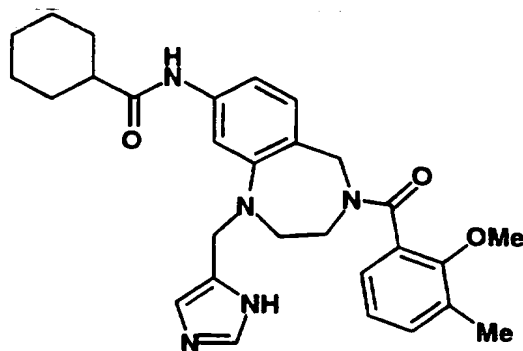


(R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[[2-(4-morpholinyl)ethyl]sulfonyl]-3-(phenylmethyl)-4H-1,4-benzodiazepine, dihydrochloride.

Example 251 was prepared from Compound A of Example 250 and morpholine as described for Example 250 (61%).

MS: (M+H)⁺ = 521.

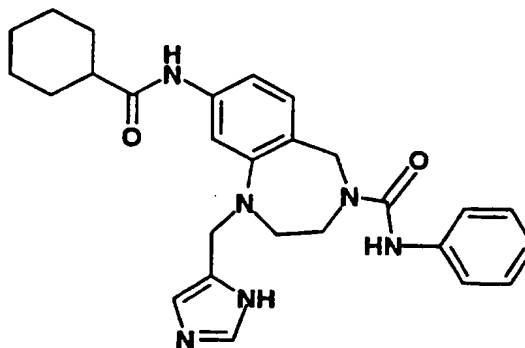
¹H NMR (CD₃OD): δ 8.9 (s, 1H), 7.75-7.2 (m, 8H), 6.95 (m, 1H), 5.0-4.4 (m, 3H), 4.1-3.7 (m, 7H), 3.5-3.1 (m, 6H), 3.0 (m, 3H), 2.85 (m, 1H), 2.55 (m, 1H).

Example 252

N-[2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(2-methoxy-3-methylbenzoyl)-1H-1,4-benzodiazepin-8-yl]cyclohexanecarboxamide, dihydrochloride.

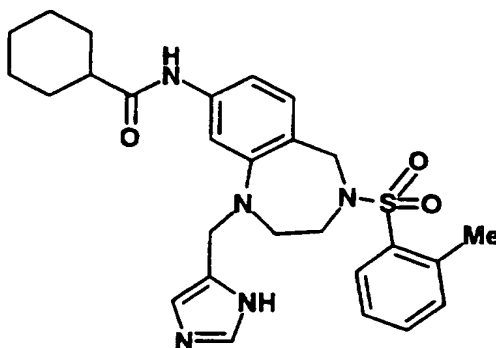
To a solution of Compound C of Example 246 (46 mg, 0.1 mmol) in DMF (1 mL) at rt under argon were added sequentially, 2-methoxy-3-methylbenzoic acid (20 mg, 0.12 mmol), DIPEA (0.09 mL, 0.5 mmol), HOAt (16 mg, 0.12 mmol) and EDC (23 mg, 0.12 mmol). After 18 hr, NaOH (1N, 1 mL) and MeOH (2 mL) were added. After 25 min, the volatiles were removed in vacuo and the residue was partitioned between chloroform (15 mL) and NaHCO₃ (10 mL). The organic layer was separated, dried and concentrated in vacuo. The residue was purified by silica gel chromatography eluting with 5% MeOH in chloroform to afford a white solid (42 mg, 83%) which was dissolved in MeOH (1 mL) and HCl in ether (1N, 2 mL) was added. The mixture was concentrated in vacuo to afford Example 252 as a yellow solid (50 mg).

MS (M+H)⁺ = 502.3.

Exempl 253

5 **8-[(Cyclohexylcarbonyl)amino]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-N-phenyl-1H-1,4-benzodiazepine-4-carboxamide, dihydrochloride.**

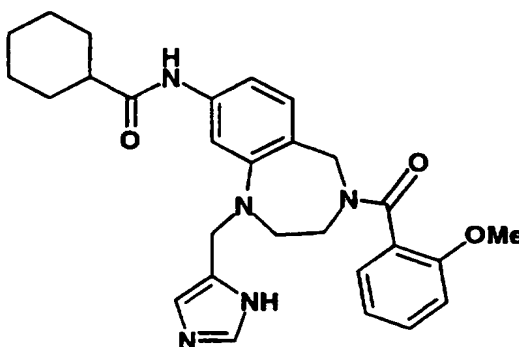
To a solution of Compound C of Example 246 (46 mg, 0.1 mmol) in DMF (1 mL) at rt under argon were added sequentially, phenylisocyanate (13 μ L, 0.12 mmol) and DIPEA (0.09 mL, 0.5 mmol). After 18 hr, NaOH (1N, 1 mL) and MeOH (2 mL) were added. After 25 min, the volatiles were removed in vacuo and the residue was partitioned between chloroform (15 mL) and water (10 mL). Some of the desired product that precipitated was filtered. The organic layer was separated and concentrated in vacuo. The residue was mixed with the solid obtained by filtration, dissolved in MeOH/TFA mixture and purified by reverse phase preparative HPLC eluting with 50%-90% aqueous MeOH containing 0.1% TFA. Appropriate fractions were collected and concentrated. The residue was treated with 1N HCl followed by concentration. After three treatments, the residue was dissolved in water and lyophilized to afford Example 253 as a yellow solid (30 mg, 55%).
MS (M+H)⁺ = 473.3.

Example 254

N-[2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[(2-methylphenyl)sulfonyl]-1H-1,4-benzodiazepin-8-yl]cyclohexanamide, dihydrochloride.

Example 254 was prepared as a yellow solid from Compound C of Example 246 and 2-methylbenzenesulfonyl chloride as described for Example 253, except that the quenched, evaporated reaction mixture was directly purified by preparative HPLC (29%).

MS (M+H)⁺ = 508.2.

Example 255

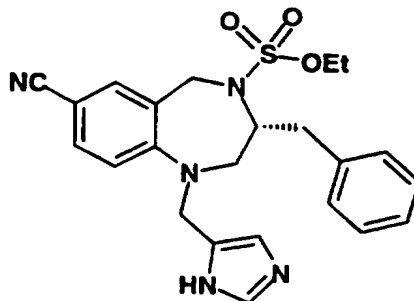
N-[2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[(2-methoxyphenyl)carbonyl]-1H-1,4-benzodiazepin-8-yl]cyclohexanamide, dihydrochloride.

Example 255 was prepared as a pale yellow solid from Compound C of Example 246 and 2-methoxybenzoic acid as described for Example 252.

MS (M+H)⁺ = 488.3.

5

Example 256



10 **(R)-7-Cyano-1,2,3,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4H-1,4-benzodiazepine-4-sulfonic acid, ethyl ester, hydrochloride.**

A. (R)-7-Cyano-1,2,3,5-tetrahydro-3-(phenylmethyl)-4H-1,4-benzodiazepine-4-sulfonic acid, ethyl ester

15 Ethyl chlorosulfonate (0.49 g, 3.41 mmol) was added to a solution of Compound C of Example 248 (0.3 g, 1.13 mmol) and DIPEA (0.78 mL, 4.55 mmol) in dichloromethane (8 mL) at 0°C under argon. After stirring for 16 hr as it warmed to rt, the mixture was diluted with chloroform and NaHCO₃. The layers were separated and the aqueous layer was extracted with chloroform. The combined organic extracts were washed with
20 NaHCO₃, water, 1N HCl and twice with brine, dried over MgSO₄, filtered and concentrated, to afford Compound A (0.54 g, 13 %). MS (M-H)⁻ = 370.

B. (R)-7-Cyano-1,2,3,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4H-1,4-benzodiazepine-4-sulfonic acid, ethyl ester, hydrochloride.

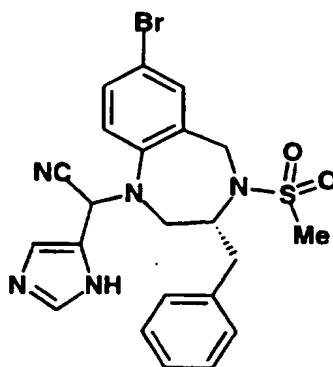
Example 256 was prepared from Compound A as described for Compound D of Example 1, using dichloroethane and 3A sieves. Purification by preparative HPLC followed by conversion to the HCl salt and
30 lyophilization afforded Example 256.

MS (M+H)⁺ = 535.

¹H NMR (400 MHz, CD₃OD): δ 8.9 (s, 1H), 7.5-7.2 (m, 8H), 6.9 (d, 1H, J = 8 Hz), 5-4.4 (m, 4H), 4.3 (m, 1H), 4-3.2 (m, 4H), 3.0 (m, 1H), 2.8 (m, 1H), 1.05 (t, 3H).

5

Example 257

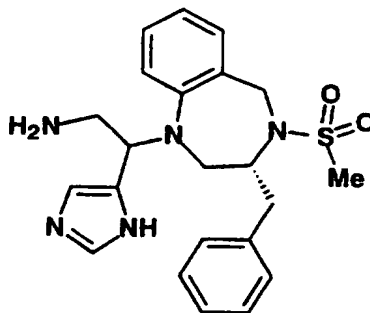


10 **(3R)-7-Bromo-1-[cyano(1H-imidazol-4-yl)methyl]-2,3,4,5-tetrahydro-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.**

To a stirred solution of Compound C of Example 224 (390 mg, 1.0 mmol) in a mixture of acetonitrile, methanol and acetic acid (3 mL, 1:1:1) was added 4-formylimidazole (100 mg, 1.04 mmol) followed by sodium cyanide (55 mg, 1.12 mmol). The mixture was stirred at room temperature for 2 days, quenched with saturated potassium carbonate (2 mL) and partitioned between ethyl acetate and 1N NH₄OH solution. The organic layer was separated and washed with brine, dried, and concentrated to give a solid (400 mg, 80%). A portion was converted to its HCl salt by dissolving in methanol, addition of 1 N HCl in ether, and removal of the solvent to afford Example 257.

TLC R_f = 0.50 (ethyl acetate, two spots)

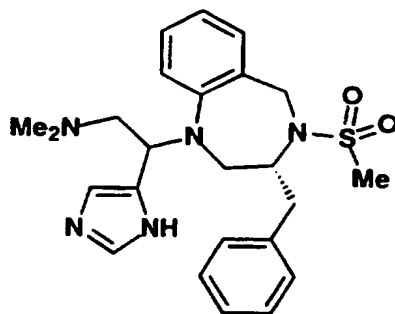
MS (M+H)⁺ 500

Example 258

(3R)-1-[2-Amino-1-(1H-imidazol-4-yl)ethyl]-2,3,4,5-tetrahydro-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.

To a stirred suspension of lithium aluminium hydride (95 mg, 2.5 mmol) in ether under argon at room temperature, was added a solution of the free base of Example 257 (250 mg, 0.5 mmol) in anhydrous THF. The mixture was stirred at room temperature for 8h and was diluted with THF, followed by ethyl acetate and ammonium hydroxide. The suspension was stirred at room temperature for 18h and filtered. The filtrate was concentrated in vacuo and the residue was purified by chromatography (ethyl acetate/methanol/NH₄OH, 10:1:0.1) on silica to give a semisolid (80 mg, 38%). A portion of it was converted to its HCl as described in Example 257.

MS (M+H)⁺ 426

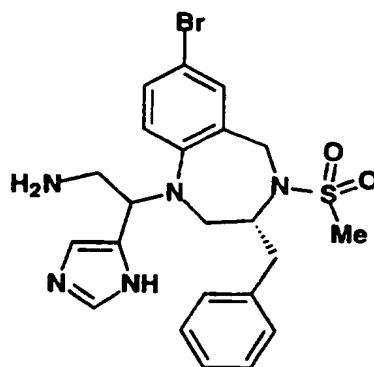
Example 259

5 **(3R)-1-[2-(Dimethylamino)-1-(1H-imidazol-4-yl)ethyl]-2,3,4,5-tetrahydro-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.**

10 To a stirred solution of the free base of Example 258 (20 mg) in methanol (1 mL) and acetic acid (0.5 mL) with sodium acetate (100 mg), was added 30 μ L of formaldehyde (37% aq. solution), followed by NaCNBH₃ (15 mg). The mixture was stirred for 15 min, additional formaldehyde (30 μ L) and NaCNBH₃ were added and the mixture was stirred for 30 min and diluted with ethyl acetate and quenched with 3 mL of NH₄OH solution. The organic layer was separated, washed with 1 N NH₄OH solution and brine,

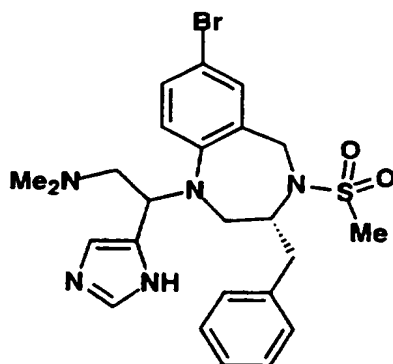
15 dried, and concentrated. The residue was converted to its HCl salt as described in Example 257 (23 mg).

MS (M+H)⁺ 454.

Exempl 260

5 **(3R)-1-[2-Amino-1-(1H-imidazol-4-yl)ethyl]-7-bromo-2,3,4,5-tetrahydro-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.**

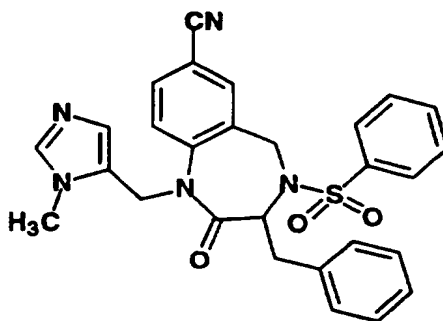
To a stirred solution of the free base of Example 258 (20 mg) in chloroform (1.5 mL) was added tetrabutylammonium perbromide. The
10 mixture was stirred at room temperature for 10 min and quenched with an aqueous solution of NaS₂O₃. The organic layer was separated and washed with chloroform. The combined organic layers were dried over MgSO₄ and concentrated in vacuo. The residue was purified by column chromatography (ethyl acetate/methanol/NH₄OH; 10:1:0.1) to give a white solid (17 mg),
15 which was converted to its hydrochloride salt as described in Example 257. MS (M+H)⁺ 504.

Example 261

- 5 **(3R)-1-[2-(Dimethylamino)-1-(1H-imidazol-4-yl)ethyl]-7-bromo-2,3,4,5-tetrahydro-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.**

Example 261 was prepared from Example 260 as described for Example 259.

- 10 MS (M+H)⁺ 532.

Example 262

- 15 **7-Cyano-1,3,4,5-tetrahydro-1-(1-methyl-1H-imidazol-5-ylmethyl)-3-(phenylmethyl)-4-(phenylsulfonyl)-2H-1,4-benzodiazepin-2-one, monohydrochloride.**

- 20 **A. (R)-N-(2-amino-5-bromo-phenylmethyl)-N-(methanesulfonyl)-phenylalanine methyl ester**

To a stirred solution of (R)-N-(2-aminophenylmethyl)-N-(methanesulfonyl)-phenylalanine methyl ester (prepared from D-

phenylalanine methyl ester hydrochloride by reductive amination with 2-nitrobenzaldehyde followed by reaction with methanesulfonyl chloride in pyridine and reduction with stannous chloride in ethyl acetate; 7.0 g, 16.5 mmol) in chloroform (75 mL) at room temperature was added

5 tetrabutylammonium perbromide (7.1 g, 14.8 mmol) portionwise. The mixture was allowed to stir at room temperature for 30 min. Saturated NaHCO₃ solution was added, followed by solid Na₂S₂O₃. The mixture was stirred for 1 hour, concentrated in vacuo, and the residue was partitioned between water and 50% ethyl acetate/hexanes. The organic layer was separated,
10 washed with water, brine, dried, concentrated in vacuo. The residue was purified by flash column chromatography to give Compound A as an oil (4.5 g, 54%). MS (M+H)⁺ 503. [α]_D²⁰: + 29.6 ° (CHCl₃, c = 0.25)

B. 7-Cyano-1,3,4,5-tetrahydro-3-(phenylmethyl)-4-(phenylsulfonyl)-2H-1,4-benzodiazepin-2-one

15 A solution of Compound A (2.05 g, 4.07 mmol) in N-methylpyrrolidinone (10 mL) in the presence of CuCN (1.1 g, 12.3 mmol) was heated at 195°C for 4 h. The mixture was cooled to room temperature and partitioned between NH₄OH solution and methylene chloride. The
20 organic layer was separated and the aqueous layer was extracted with methylene chloride. The combined organic layers were washed with brine, dried, and concentrated. The residue was crystalized from methanol to give Compound B as a brown solid (1.1 g, 65%). MS(M+H)⁺ 416. mp 222-223°C.

25

C. 7-Cyano-1,3,4,5-tetrahydro-1-(1-triphenylmethyl-1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(phenylsulfonyl)-2H-1,4-benzodiazepin-2-one

To a stirred solution of Compound B (310 mg, 0.74 mmol), N-tritylimidazole-4-methanol (510 mg, 1.5 mmol) and triphenylphosphine (450 mg, 1.72 mmol) in toluene and dichloroethane (20 mL/3 mL) at 60°C under argon, was added diethylazodicarboxylate (300 μL, 1.9 mmol). The mixture was stirred at 60°C for 1 h and partitioned between ethyl acetate and water. The organic layer was washed with water and brine, dried, concentrated in
30 vacuo, and purified by flash column chromatography (ethyl acetate/hexanes 2:3) to give Compound C as an oil (450 mg, 82%). MS(M+H)⁺ 740.

35

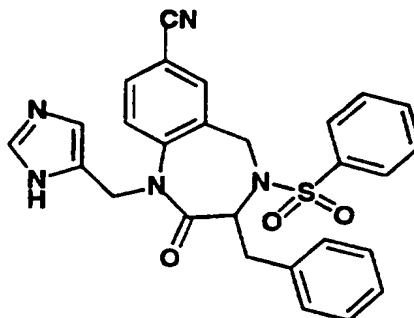
D. 7-Cyano-1,3,4,5-tetrahydro-1-(1-methyl-1H-imidazol-5-ylmethyl)-3-(phenylmethyl)-4-(phenylsulfonyl)-2H-1,4-benzodiazepin-2-one, monohydrochloride

To a stirred solution of Compound C (210 mg, 0.28 mmol) in THF at room temperature under argon, was added methyl trifluoromethylsulfonate (35 μ L, 0.31 mmol). The mixture was stirred at room temperature for 10 min. Acetic acid (0.5 mL) and triethylsilane (0.25 mL) were added. The mixture was heated at 60°C for 30 min and partitioned between 1 N NaOH and ethyl acetate. The organic layer was separated and washed with brine, dried and concentrated in vacuo. The residue was purified by flash column chromatography to give the free base of Compound D an oil (100 mg, 71%). This was dissolved in methanol, and 1N HCl solution in ether was added. The solvent was removed to give Example 262 as a solid.

MS (M+H)+512.

mp: 160°C

Example 263



20 7-Cyano-1,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(phenylsulfonyl)-2H-1,4-benzodiazepin-2-one, monohydrochloride.

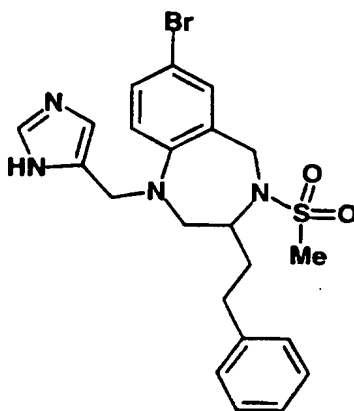
To a stirred solution of Compound C of Example 262 (200 mg, 0.27 mmol) in CHCl_3 at room temperature under argon, was added trifluoroacetic acid (1 mL), followed by triethylsilane (0.5 mL). The mixture was stirred at room temperature for 2 h and partitioned between 1 N NH_4OH and ethyl acetate. The organic layer was separated and washed with brine, dried and concentrated in vacuo. The residue was purified by flash column chromatography (ethyl acetate, methanol; 95:5) to give the free base of

Example 263 as an oil (110 mg, 82%). This was dissolved in methanol, and 1N HCl solution in ether was added. The solvent was removed to give Example 263 as a solid.

MS (M+H)+498.

5 mp: 195°C

Example 264



10 **7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methanesulfonyl)-3-(2-phenylethyl)-1H-1,4-benzodiazepine, dihydrochloride.**

15 **A. 7-Bromo-2,3,4,5-tetrahydro-3-(2-phenylethyl)-1H-1,4-benzodiazepine**

Compound A was prepared from D,L-homoPhe and 6-bromoisatoic anhydride as described in the following sequence: Compound A of Example 80, except that DMF was used instead of pyridine, and heating was at 50°C for 24 hours; Compound B of Example 80; Compound C of Example 80.

20

B. 7-Bromo-2,3,4,5-tetrahydro-4-(methanesulfonyl)-3-(2-phenylethyl)-1H-1,4-benzodiazepine

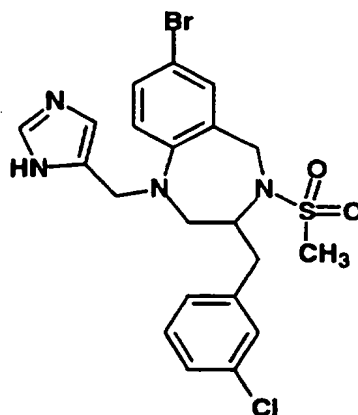
Compound A (100 mg, 0.30 mmol) was dissolved in THF (5 mL) and DIEA (211 µL, 1.21 mmol) was added followed by methanesulfonyl chloride (94 µL, 1.21 mmol). The solution was stirred for 30 min, concentrated, redissolved in ethyl acetate (50 mL) and washed with water (3X20 mL). The organic layer was dried (Na₂SO₄) and concentrated to yield Compound B as a light brown glass.

25

C. 7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(2-phenylethyl)-1H-1,4-benzodiazepine, dihydrochloride

Compound C and 4-formylimidazole were dissolved in 1,2-DCE (5 mL) and acetic acid (0.5 mL) and sodium triacetoxyborohydride was added. The mixture was stirred at 50°C for 2h and saturated NaHCO₃ (5 mL) was added. The mixture was concentrated and the residue was partitioned between water (20 mL) and ethyl acetate (20mL). The organic layer was washed with water (10mL), brine (10 mL), dried (MgSO₄), concentrated and purified by preparative HPLC (gradient of aq methanol, 0.1% TFA). Appropriate fractions were combined, concentrated and lyophilized. The lyophilate was dissolved in methanol (0.5 mL) and 1N HCl (5mL). The mixture was concentrated and lyophilized. This procedure was repeated to provide Example 264 as a white solid (15 mg, 19%). MS (M+H)⁺ 490.

Example 265



20 7-Bromo-3-[(3-chlorophenyl)methyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-1H-1,4-benzodiazepine, dihydrochloride.

25 A. 2-[2-(1,1-dimethyl-ethoxycarbonylamino)-3-(3-chlorophenyl)-propylamino]-5-bromobenzoic acid

N-Boc-3-chloro-phenylalaninal (800 mg, 2.8 mmol) and 2-amino-5-bromobenzoic acid (660 mg, 3.06 mmol) were dissolved in MeOH (10 mL). Molecular sieves (3 A, 7.0 g) and glacial acetic acid (0.2 mL) were added and the mixture was stirred for 30 min. Sodium cyanoborohydride (200 mg,

2.99 mmol) was added portionwise over 30 min. The mixture was stirred for 16 h, cooled to 0°C and saturated NaHCO₃ (30 mL) was slowly added. The mixture was stirred for 30 min, concentrated and extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with water (100 mL), brine (100 mL), dried (MgSO₄), and concentrated. Preparative HPLC (gradient of aq methanol, 0.1% TFA) afforded Compound A as a clear oil (100 mg, 7%). MS (M+H)⁺ 481.

B. 2-[2-amino-3-(3-chloro-phenyl)-propylamino]-5-bromobenzoic acid

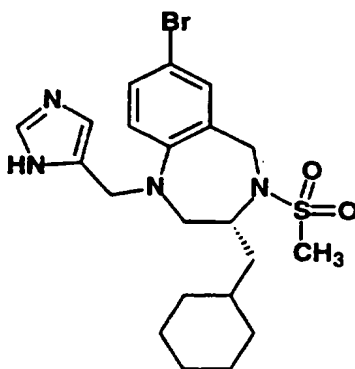
Compound A (100 mg, 0.21 mmol) was stirred in dimethyl sulfide (0.1 mL) and 4N HCl in dioxane (10 mL) for 40 min. The mixture was concentrated, redissolved in methylene chloride (20 mL) and concentrated. This latter procedure was repeated three times to yield Compound B as a clear glass.

C. 7-Bromo-3-[(3-chlorophenyl)methyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-1H-1,4-benzodiazepine, dihydrochloride.

Compound C was prepared as a white solid from Compound B by the following sequence: Compound B of Example 80; Compound C of Example 80; Compound B of Example 264; Compound C of Example 264. MS (M+H)⁺ 510.

25

Example 266



(R)-7-Bromo-3-(cyclohexylmethyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-1H-1,4-benzodiazepine, dihydrochloride.

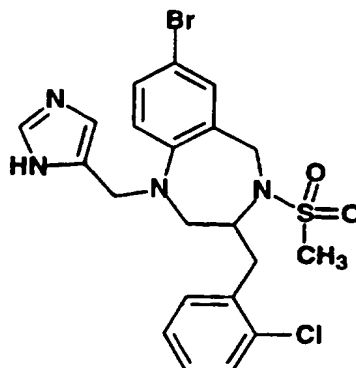
30

Example 266 was prepared as a white solid from D-N-Boc-cyclohexylalaninal as described in Example 265.

MS (M+H)⁺ 510.

5

Example 267

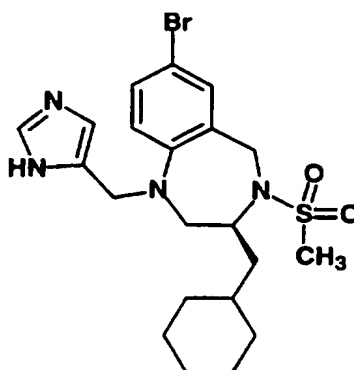


10 **7-Bromo-3-[(2-chlorophenyl)methyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-1H-1,4-benzodiazepine, dihydrochloride.**

Example 267 was prepared as a white solid from D,L-N-Boc-2-chlorophenylalaninal as described in Example 265.

15 MS (M+H)⁺ 510.

Example 268



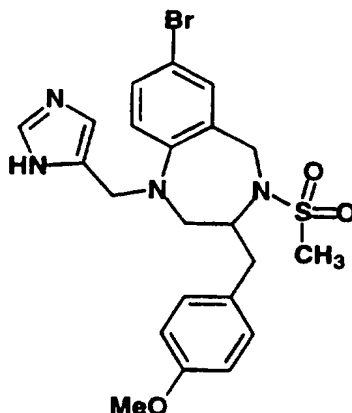
20 **(S)-7-Bromo-3-(cyclohexylmethyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-1H-1,4-benzodiazepine, dihydrochloride .**

Example 268 was prepared as a white solid from L-N-Boc-cyclohexylalaninal as described in Example 265.

MS (M+H)⁺ 482.

5

Example 269



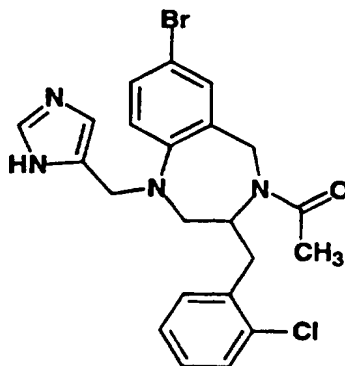
10 **7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-[(4-methoxyphenyl)methyl]-4-(methylsulfonyl)-1H-1,4-benzodiazepine, dihydrochloride.**

Example 269 was prepared as a white solid from D,L-N-Boc-4-methoxy-phenylalaninal as described in Example 265.

MS (M+H)⁺ 506.

15

Example 270



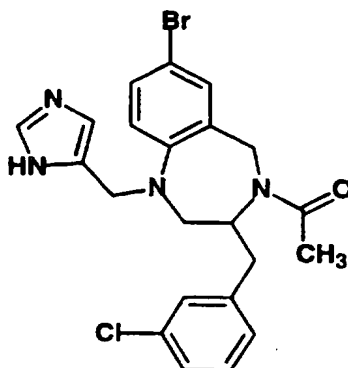
20 **4-Acetyl-7-bromo-3-[(2-chlorophenyl)methyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.**

Example 270 was prepared as a white solid from 7-bromo-3-[(2-chlorophenyl)methyl]-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine as described in Compounds D and E of Example 80.

MS (M+H)⁺ 475.

5

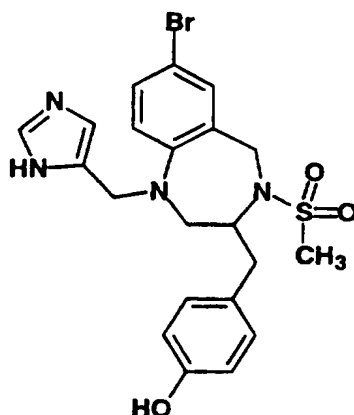
Example 271



10 **4-Acetyl-7-bromo-3-[(3-chlorophenyl)methyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.**

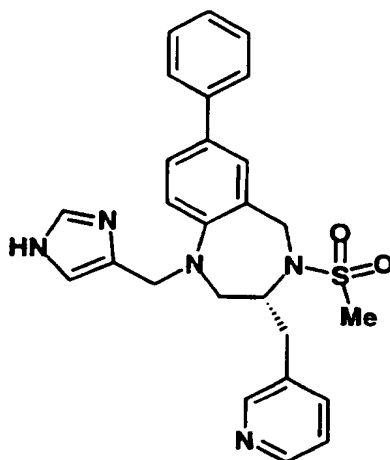
15 Example 271 was prepared as a white solid from 7-bromo-3-[(3-chlorophenyl)methyl]-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine as described in Example 270.

MS (M+H)⁺ 475.

Example 272

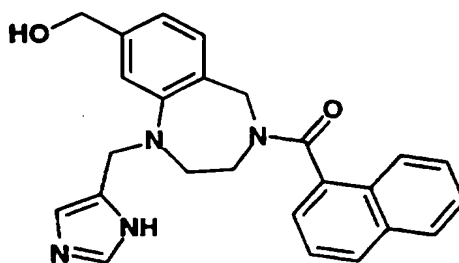
5 **7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-[(4-hydroxyphenyl)methyl]-4-(methylsulfonyl)-1H-1,4-benzodiazepine, dihydrochloride.**

To a solution of Example 269 (30 mg, 0.059 mmol) in a mixture of dichloromethane (5 mL) and 1,2-dichloroethane (5 mL) was added a
10 solution of BBr_3 (1M in dichloromethane, 0.5 mL). The mixture was stirred for 16h and 5% ammonium hydroxide (10 mL) was added. The mixture was stirred for additional 1h, concentrated and the residue purified by preparative HPLC (gradient of aqueous methanol with 0.1% TFA). Appropriate
15 fractions were combined, concentrated and lyophilized. This lyophilate was dissolved in methanol (0.5 mL) and 1N HCl (5mL). This mixture was concentrated and lyophilized. This procedure was repeated to provide Example 272 as a white solid (20 mg, 60%).
MS $(\text{M}+\text{H})^+$ 490.

Exempl 273

5 **(R)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-7-phenyl-3-(3-pyridinylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.**

Example 273 was prepared as a light yellow solid from D-pyridylalanine and Compound B of Example 226 using the following
 10 sequence: Compound C of Example 226; Compound D of Example 226; Compound B of Example 264; Compound C of Example 264.
 MS (M+H)⁺ 474.

Example 274

15 **2,3,4,5-Tetrahydro-8-(hydroxymethyl)-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, dihydrochloride.**

20 **A. 8-[2,3,4,5-Tetrahydro-1H-1,4-benzodiazepin-2,5-dionyl]-carboxylic acid**

A mixture of 7-carboxyisatoic anhydride (prepared from triphosgene and 4-carboxylic-2-amino-benzoic acid, 20 g, 0.09 mol) and

ethyl glycine hydrochloride (13.5 g, 0.097 mol) in anhydrous pyridine (200 mL) was refluxed 30 hrs and cooled to rt. The pyridine was evaporated and the residue was washed with water followed by EtOAc. The solid was dried under reduced pressure to give Compound A (17.5 g, 88%) as a white solid.

5

B. 2,3,4,5-Tetrahydro-8-(hydroxymethyl)-1H-1,4-benzodiazepine

Borane (1.0 M in THF, 1L) was added to a suspension of Compound A (10 g, 45 mmol) in ethylene glycol dimethyl ether (10 mL). The suspension was stirred at r.t. for 1 hr, refluxed for 8 hrs, cooled to 0° and quenched with 6N HCl (20 mL). The solvent was evaporated, the residue dissolved in water (30 mL) and the mixture neutralized with sat. Na₂CO₃ and evaporated. The residue was evaporated from methanol and purified by flash column chromatography (10% MeOH, 1% NH₄OH in CH₂Cl₂) to provide Compound B as a white solid. MS (M+H)⁺ 179.

10

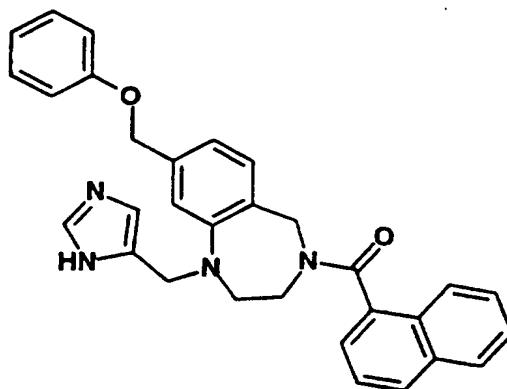
15

C. 2,3,4,5-Tetrahydro-8-(hydroxymethyl)-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, dihydrochloride

20

Example 274 was prepared as an off white solid from Compound B as described for Compound F of Example 41, with chromatography using 5% MeOH/0.5% NH₄OH/methylene chloride, and Compound D of Example 1, with purification by prep HPLC before formation of the HCl salt. MS (M+H) 413.

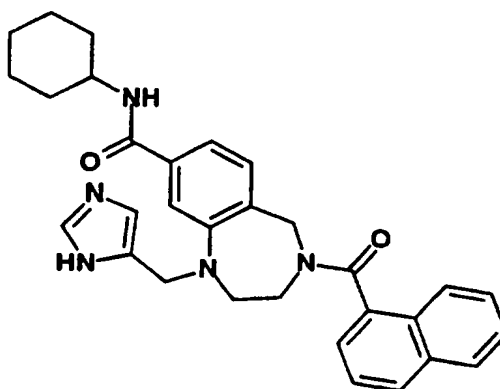
25

Exempl 275

5 **2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-8-(phenoxymethyl)-1H-1,4-benzodiazepine, dihydrochloride.**

10 A solution of Example 274 (0.38 g, 0.9 mmol) and Boc_2O (1.2 g, 5.4 mmol) in CH_2Cl_2 (10 mL) was stirred for 48 hrs and evaporated. The residue was purified by flash chromatography (4% MeOH in CH_2Cl_2) to give the protected imidazole analog as a white solid (0.190 g, 40%). A mixture of a portion of this material (42 mg, 0.08 mmol), Ph_3P (28 mg, 0.1 mmol), phenol (30 mg, 0.3 mmol) and diethylazodicarboxylate (0.05 mL, 0.3 mmol) in THF (7 mL) was stirred for 48 hrs. under N_2 . 1N HCl (5 mL) was added. The mixture was stirred for 1 hr and evaporated. The residue was treated with 6M HCL, extracted with CH_2Cl_2 (2X10 mL) and the aqueous layer evaporated to give a solid which was purified by prep HPLC (gradient of aqueous methanol with 0.1% TFA) and converted into its HCl salt by lyophilization from 1M HCl (5 mL) to give Example 275 as a white solid (10 mg, 24%)

20 MS (M+H)⁺ 489.

Example 276

N-Cyclohexyl-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine-8-carboxamide, dihydrochloride.

A. 2,3,4,5-Tetrahydro-8-(hydroxymethyl)-1H-1,4-bis-(1-naphthalenylcarbonyl)-benzodiazepine

Naphthoyl chloride (18 mL g, 110 mmol) was added to a solution of compound B of Example 274 (24 g, 29 mmol) in pyridine (150 mL) and the resulting solution was stirred for 10 hrs and poured into ice-water. The resulting precipitate was filtered and the solid was washed with water and subjected to flash chromatography (3% MeOH in CH₂Cl₂) to provide the trinaphthoate as a yellow solid (8.4 g, 45%). A portion of this material (5.63 g, 87 mmol) in MeOH (60 mL) was stirred with 1M NaOMe in MeOH (40 mL) for 10 hrs and evaporated. The residue was dissolved in CH₂Cl₂ (150 mL) and the solution was washed with H₂O (50 mL) and 1N HCL (50 mL), dried over Na₂SO₄ and evaporated. Purification by flash chromatography (5% MeOH in CH₂Cl₂) provided Compound A as a white solid (3.8 g, 89%). MS (M+H)⁺ 486.

B. 2,3,4,5-Tetrahydro-1-(1-naphthalenylcarbonyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine-8-carboxylic acid

Jones reagent (5% CrO₃ in 10% H₂SO₄ in H₂O, 15 mL) was slowly added to a solution of Compound A (2.7 g, 5.6 mmol) in acetone (50 mL) at 0°C. The solution was stirred for 1hr. at r.t. The excess CrO₃ was destroyed by adding iPrOH. The aqueous solution was extracted with CH₂Cl₂ (3X 100 mL). The combined organic phases were dried over Na₂SO₃ and evaporated to give a solid which was purified by flash chromatography (5%

MeOH in CH_2Cl_2) to provide Compound B as a solid (2.30 g, 82.7%). MS $(\text{M}+\text{H})^+$ 499.

5 **C. 2,3,4,5-Tetrahydro-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine-8-carboxylic acid**

A mixture of Compound B (1.02 g, 2 mmol) in MeOH (40 mL) was refluxed with KOH (7.75 g, 138 mmol) in H_2O (10 mL) for 40 hrs. The MeOH was evaporated and aqueous solution was neutralized with conc. HCl. The resulting precipitate was filtered and washed with H_2O . The solid was dried to provide Compound C as a white solid (0.635 g, 90%). MS $(\text{M}+\text{H})^+$ 347.

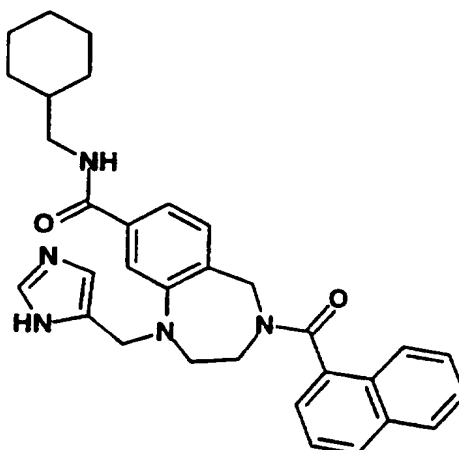
D. N-Cyclohexyl-2,3,4,5-tetrahydro-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine-8-carboxamide

A solution of cyclohexylamine (0.32 g, 3.2 mmol) and diisopropylethylamine (1 mL, 5.7 mmol) in DMF (1 mL) was added to a solution of EDC (0.12 g, 0.62 mmol), HOBT (0.13 g, 0.9 mmol) and Compound C (20 mg, 0.06 mmol) in DMF (5 mL). The solution was stirred for 24 hrs and evaporated. The residue was dissolved in EtOAc (20 mL) and the solution was washed with sat. NaHCO_3 , 1N HCl (5 mL), dried over Na_2SO_4 and evaporated to give Compound D as a pale yellow solid (40 mg).

E. N-Cyclohexyl-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine-8-carboxamide, dihydrochloride

25 Compound E was prepared from Compound D as described for Compound D of Example 1, with purification by prep HPLC before formation of the HCl salt.

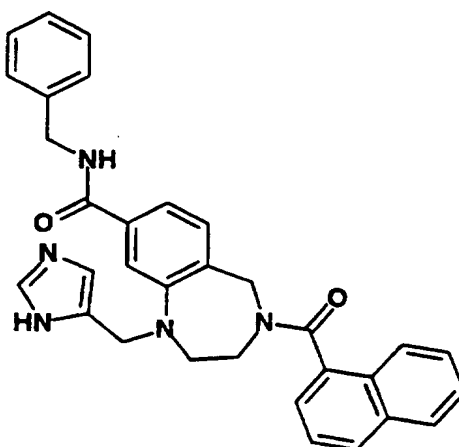
MS $(\text{M}+\text{H})^+$ 508.

Example 277

5 **N-(Cyclohexylmethyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine-8-carboxamide, dihydrochloride.**

Example 277 was prepared as an off white solid from Compound C of Example 276 and cyclohexylamine as described in Compounds D and E of Example 276.

10 MS (M+H)⁺ 522.

Example 278

15

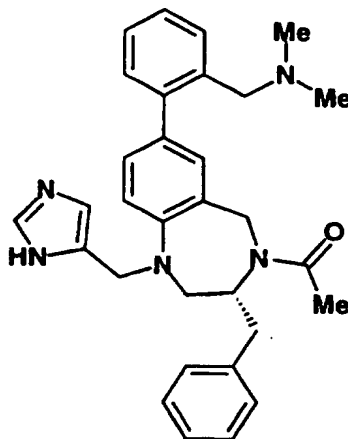
2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-N-(phenylmethyl)-1H-1,4-benzodiazepine-8-carboxamide, dihydrochloride .

Example 278 was prepared as an off white solid from Compound C of Example 276 and benzylamine as described in Compounds D and E of Example 276.

MS (M+H)⁺ 517.

5

Example 279



10 **(R)-4-Acetyl-7-[2-[(dimethylamino)methyl]phenyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.**

A. 2-[(R)-2,3,4,5-tetrahydro-3-(phenylmethyl)-1H-1,4-benzodiazepin-2,5-dione-7-yl]-benzaldehyde

15 Compound A was prepared as a yellow solid from Compound A of Example 224 and 4-formylbenzeneboronic acid as described for Compound A of Example 12, with THF as solvent, refluxing for 10 hours, and extractive workup. MS (M+H)⁺ 371.

20 **B. (R)-7-(2-(Dimethylaminomethyl)-phenyl)-2,3,4,5-tetrahydro-3-(phenylmethyl)-1H-1,4-benzodiazepin-2,5-dione**

A solution of Compound A and dimethylamine (1.0 M in THF, 10 mL) in 1:10/AcOH:CH₂Cl₂ (20 mL) was stirred for 1 hr. NaBH(OAc)₃ (2.0 g) was added. Stirring was continued for 14 hrs. The solvent was evaporated and residue was treated with 1N NaOH (10 mL). The aqueous layer was
25 extracted with 10% iPrOH in CH₂Cl₂. The organic phase was dried and evaporated to give a pale yellow solid which was purified by flash

chromatography (10% MeOH, 1% Et₃N in CH₂Cl₂) to provide Compound B as a white solid (1.13 g, 98%). MS(M+H)⁺ 400.

5 **C. (R)-7-(2-(Dimethylaminomethyl)-phenyl)-2,3,4,5-tetrahydro-3-(phenylmethyl)-1H-1,4-benzodiazepine**

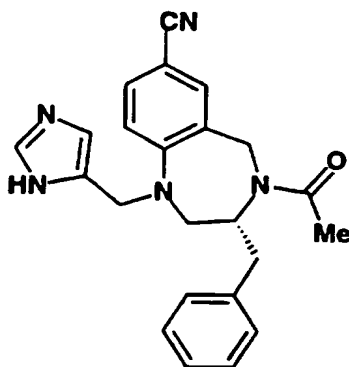
A solution of Compound B (1.13 g) in dry THF was treated with LAH (1.0 M in THF, 15 mL) at 0° C. The solution was refluxed for 10 hrs, cooled to 0° C and H₂O (5 mL) was added followed by THF (10 mL) and 20% NaOH (5 mL). The THF solution was decanted and the solid was washed with THF.
10 The combined THF solutions were evaporated and the residue dissolved in CH₂Cl₂ (20 mL). The solution was evaporated to give Compound C as a pale yellow solid (0.7 g, 67%). MS (M+H)⁺ 372.

15 **D. (R)-4-Acetyl-7-[2-[(dimethylamino)methyl]phenyl]-2,3,4,5-tetrahydro-3-(phenylmethyl)-1H-1,4-benzodiazepine**

Acetyl chloride (0.03 mL, 1.1 eq.) in CH₂Cl₂ (0.3 mL) was added to a solution of Compound C (0.155 g, 0.41 mmol) and DIEA (0.4 mL, 2.7 mmol) in CH₂Cl₂ (10 mL). The mixture was stirred 20 minutes and evaporated. The residue was dissolved in EtOAc and the solution was
20 washed with sat. NaHCO₃, dried over Na₂SO₄ and evaporated to give Compound D as an oil (0.14 g, 84%).

25 **E. (R)-4-Acetyl-7-[2-[(dimethylamino)methyl]phenyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.**

Compound E was prepared from Compound D as described for Compound E of Example 276.
MS (M+H)⁺ 492.

Exempl 280

5 **(R)-4-Acetyl-7-cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.**

A. **(R)-7-Cyano-2,3,4,5-tetrahydro-3-(phenylmethyl)-4-[(1,1-dimethylethoxy)-carbonyl]-1H-1,4-benzodiazepine**
10 Compound A was prepared as a white solid from Compound C of Example 248 as described for Compound A of Example 4, with stirring in THF for 10 hours.

B. **(R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-[(1,1-dimethylethoxy)-carbonyl]-1H-1,4-benzodiazepine**
15 Compound B was prepared from Compound A as described for Compound D of Example 1.

20 C. **(R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine**
Compound C was prepared from Compound B by treatment with 4M HCl in 4:1 ethyl acetate:dioxane. MS(M+H)⁺ 244.

25 D. **(R)-4-Acetyl-7-cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride**

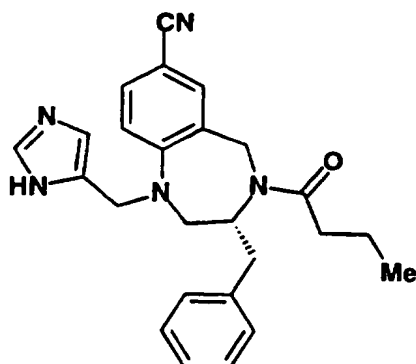
Compound D was prepared from Compound C by treatment with DIEA, EDC, HOBT and acetic acid in DMF for 14 hours. Purification by prep

HPLC (gradient of aqueous methanol with 0.1% TFA) and conversion into its HCl salt by lyophilization from 1M HCl afforded Example 280 as a solid.

MS (M-H)⁺ 386.

5

Example 281

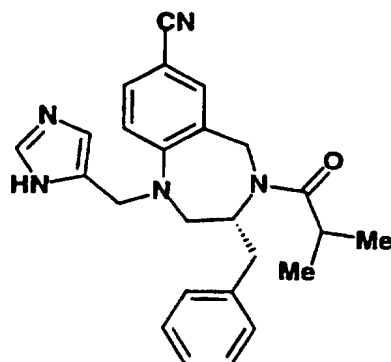


10 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-oxobutyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.

Example 281 was prepared as a solid from Compound C of Example 280 and butyric acid as described for Compound D of Example 280.

15 MS (M-H)⁺ 414.

Example 282



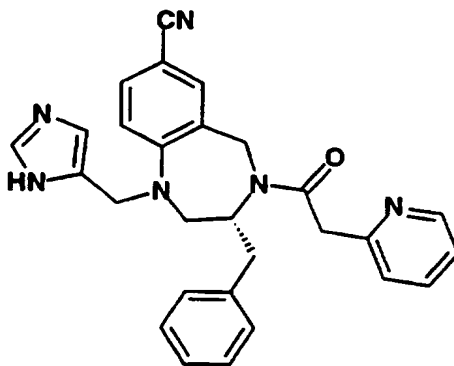
20 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(2-methyl-1-oxopropyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.

Example 282 was prepared as a solid from Compound C of Example 280 and isobutyric acid as described for Compound D of Example 280.

MS (M-H)⁺ 414.

5

Example 283



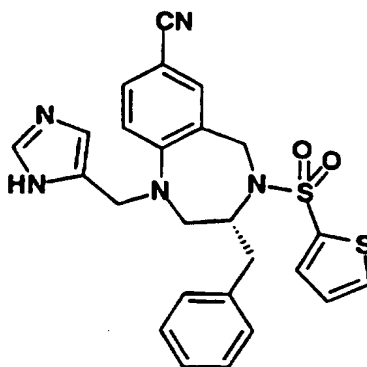
10

(R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(2-pyridinylacetyl)-1H-1,4-benzodiazepine, dihydrochloride.

15

Example 283 was prepared as an off white solid from Compound C of Example 280 and 2-pyridylacetic acid as described for Compound D of Example 280.

MS (M-H)⁺ 464.

Example 284

5 **(R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(2-thienylsulfonyl)-1H-1,4-benzodiazepine, monohydrochloride.**

A. (R)-7-Cyano-2,3,4,5-tetrahydro-3-(phenylmethyl)-4-(2-thienylsulfonyl)-1H-1,4-benzodiazepine

10 2-Thiophenesulfonyl chloride (34.56 g, 0.19 mol) in CH_2Cl_2 (200 mL) was added to a solution of Compound C of Example 248 (37.4 g, 0.142 mol) and DIEA (38 mL, 0.23 mol) in CH_2Cl_2 (500 mL) at rt. The solution was stirred for 48 hrs and evaporated. The residue was partitioned between CH_2Cl_2 (500 mL) and saturated NaHCO_3 (2x500 mL). The organic layer was
15 dried (Na_2SO_4) and evaporated. The residual yellow oil was purified by flash chromatography (20% followed by 50%ethyl acetate/hexanes) to provide Compound A as a yellow solid (55 g, 95%).

20 **B. (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(2-thienylsulfonyl)-1H-1,4-benzodiazepine, monohydrochloride.**

A mixture of Compound A (55 g, ~0.134 mol) and 4-formylimidazole (51 g, 0.53 mol) in $\text{AcOH}/\text{CH}_2\text{ClCH}_2\text{Cl}$ (140 mL/600 mL) was stirred for 50 min at 55°C under N_2 . $\text{NaBH}(\text{OAc})_3$ (total: 72 g, 0.34 mol) was
25 added over 15 hrs (every 1.5 to 2 hrs, average about 6 g was added) until HPLC analysis showed the absence of Compound A. MeOH (250 mL) was added and the solvent was evaporated. The residue was stirred with H_2O

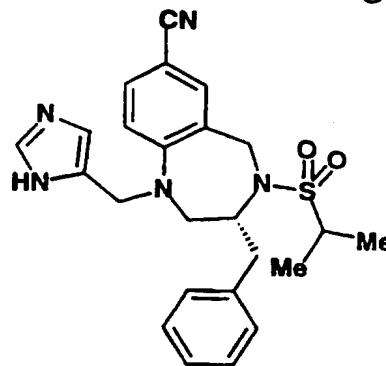
- (100 mL), then 4% NaOH (800 mL) for 30 min. The aqueous solution was extracted with ethyl acetate (2x800 mL). The combined organic layers were washed with 5% NaOH (800 mL) and dried over Na₂SO₄. Evaporation of solvent gave an oil (85g) which was purified by flash chromatography (silica, 5% MeOH in EtOAc) to provide 70 g of a wet solid. HCl (1.0 M in ether, 400 mL, 0.4 mol) was added to a solution of the solid in EtOAc (600 mL). The resulting suspension was stirred for 20 min and evaporated. The residue was washed with EtOAc (2x500 mL) and ether (2x100 mL) and dried under high vacuum to provide Compound B (63 g, 83%) as an off white solid.
- 10 MS (M+H)⁺ 490.
- ¹H-NMR (CD₃OD, 300 MHz) δ 2.90 (m, 2H), 3.15 (m, 2H), 3.90 (m, 1H), 4.3 to 5.1 (m, 4H), 6.40 (d, 7Hz, 1H), 7.0 to 7.6 (m, 11H), 8.90 (s, 1H).

Examples 285-295

Examples 285-295 were prepared from Compound C of Example 248 (Exs 285, 286, 291, 292, 293, 294, 295), Compound B of Example 224 (Exs 287, 288) or Compound B of Example 232 (Exs 289, 290) and the appropriate sulfonyl chloride as described for Example 284.

Example

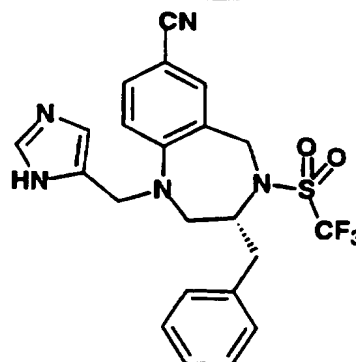
285 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[(1-methylethyl)sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride. BMS-214665



Mass
Spectrum

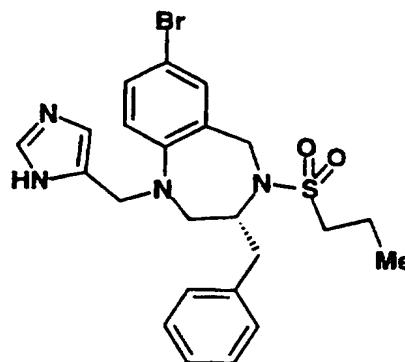
m/z
450
(M+H)

286 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-[(trifluoromethyl)sulfonyl]-1H-1,4-benzodiazepine, monohydrochloride. BMS-214666

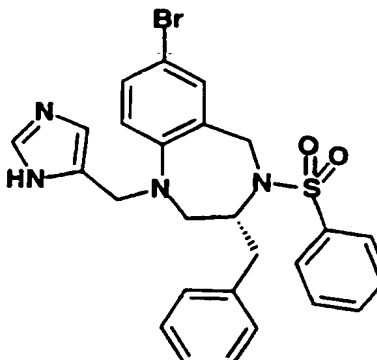
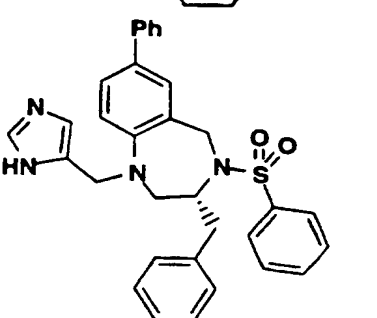
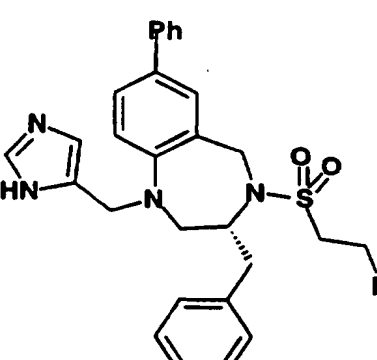
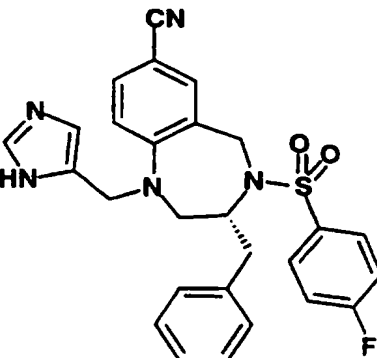


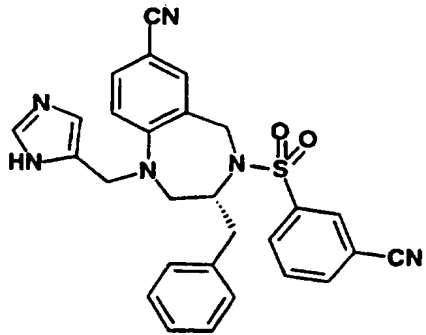
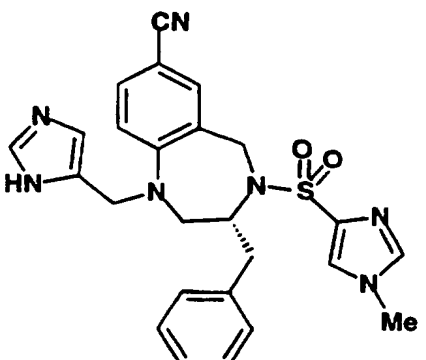
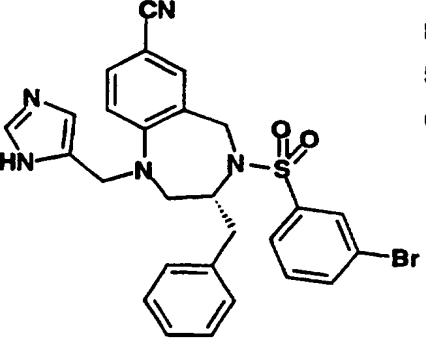
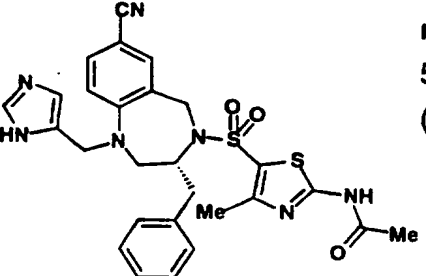
m/z
476
(M+H)

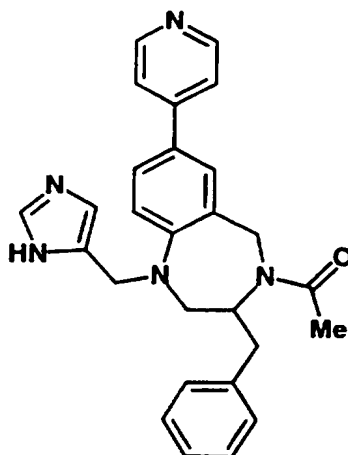
287 (R)-7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(propylsulfonyl)-1H-1,4-benzodiazepine, monohydrochloride. BMS-215354



m/z
501
(M+H)

- 288 (R)-7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(phenylsulfonyl)-1H-1,4-benzodiazepine, monohydrochloride. BMS-215355
- 
- m/z
539
(M+H)
- 289 (R)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-3-(phenylmethyl)-4-(phenylsulfonyl)-1H-1,4-benzodiazepine, monohydrochloride. BMS-215356
- 
- m/z
535
(M+H)
- 290 (R)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-3-(phenylmethyl)-4-(propylsulfonyl)-1H-1,4-benzodiazepine, monohydrochloride. BMS-215357
- 
- m/z
501
(M+H)
- 291 (R)-7-Cyano-4-[(4-fluorophenyl)sulfonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride. BMS-218319
- 
- m/z
502
(M+H)

- 292 (R)-7-Cyano-4-[(3-cyanophenyl)sulfonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride. BMS-218320
- 
- m/z 509 (M+H)
- 293 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[(1-methyl-1H-imidazol-4-yl)sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride. BMS-218322
- 
- m/z 488 (M+H)
- 294 (R)-4-[(3-Bromophenyl)sulfonyl]-7-cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride. BMS-218735
- 
- m/z 563 (M+H)
- 295 (R)-N-[5-[[7-cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepin-4-yl]sulfonyl]-4-methyl-2-thiazolyl]acetamide, dihydrochloride. BMS-218736
- 
- m/z 562 (M+H)

Example 296

4-Acetyl-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-7-(4-pyridinyl)-1H-1,4-benzodiazepine, trihydrochloride.

A. 4-Acetyl-2,3,4,5-tetrahydro-1-trifluoroacetyl-3-(phenylmethyl)-7-bromo-1H-1,4-benzodiazepine

Acetyl chloride (35 mL, 0.47 mmol) was added to a solution of Compound B of Example 75 (0.32 mmol, 100 mg) and NEt_3 (220 mL, 1.58 mmol) in 5 mL of CH_2Cl_2 at 0°C . After 5 minutes, trifluoroacetic anhydride (0.63 mmol, 90 mL) was added, and the reaction was stirred for an additional 10 minutes, concentrated and the residue purified by flash chromatography (50% EtOAc/Hexanes) to afford Compound A as a white solid (140 mg, 98% for two steps). MS (M+H) 455.

B. 4-Acetyl-2,3,4,5-tetrahydro-1-trifluoroacetyl-3-(phenylmethyl)-7-(4-pyridinyl)-1H-1,4-benzodiazepine

A mixture of Compound A (0.27 mmol, 124 mg), 4-tributylstannylpyridine (0.54 mmol, 200 mg) and 15 mol% $\text{Pd}(\text{PPh}_3)_4$ (47 mg) in 3 mL of toluene was degassed and heated to reflux under argon. After 16 hours, the reaction was concentrated and purified by flash chromatography (10% EtOAc/Hexanes) to isolate Compound B as a yellow oil (60 mg, 49%). MS (M+H) 454.

C. 4-Acetyl-2,3,4,5-tetrahydro-3-(phenylmethyl)-7-(4-pyridinyl)-1H-1,4-benzodiazepine

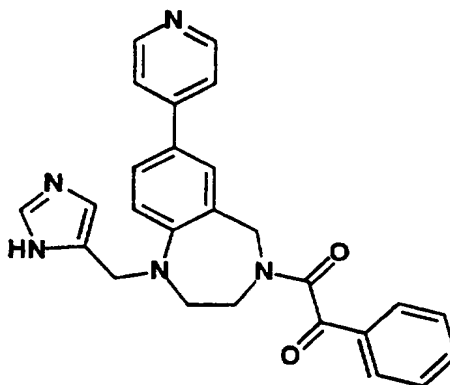
NaOH (5 drops of 2N NaOH aqueous solution) was added to a solution of Compound B (60 mg, 0.13 mmol) in 3 mL MeOH and the mixture was maintained at rt for 30 minutes, concentrated and partitioned between 2N NaOH (5 mL) and 10%isopropanol-CH₂Cl₂ (5 mL). The aqueous layer was extracted 3 times with 10%isopropanol-CH₂Cl₂ and the combined organic layers were dried over Na₂SO₄ and concentrated to afford Compound C.

D. 4-Acetyl-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-7-(4-pyridinyl)-1H-1,4-benzodiazepine, trihydrochloride

To a mixture of Compound D in 2 mL of 1:1 AcOH:ClCH₂CH₂Cl was added 4-formylimidazole (0.39 mmol, 38 mg) and NaBH(OAc)₃ (0.39 mmol, 83 mg). The mixture was heated at 50°C for 4 hours, concentrated and partitioned between 2N NaOH and 10%isopropanol/CH₂Cl₂ (5 mL). The aqueous layer was extracted 3 times with 10%isopropanol-CH₂Cl₂ and the combined organic layers were dried over Na₂SO₄, concentrated and purified by prep HPLC (gradient of aqueous methanol with 0.1% TFA). The TFA salt was converted to the HCl salt with 1N HCl to afford Example 296 as a yellow solid (32 mg, 49% from Compound B).

MS (M+H) 438.

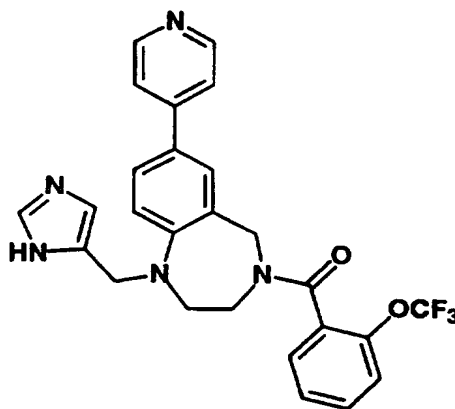
Example 297



2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(2-phenyl-1,2-dioxoethyl)-7-(4-pyridinyl)-1H-1,4-benzodiazepine, trihydrochloride.

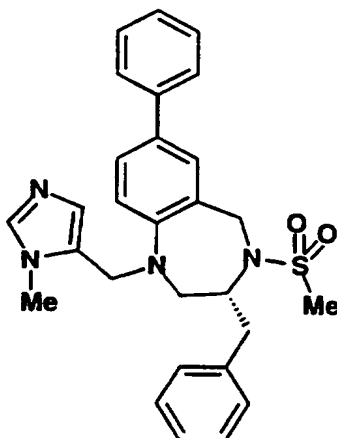
Example 297 was prepared as a yellow solid from 7-bromo-1,4-benzodiazepine (see Example 11) and benzoylformic acid by the following sequence: Example 252, in 10:1 methylene chloride:DMF and with chromatography with 50%EtOAc/hexanes; treatment with trifluoroacetic anhydride and workup as described in Compound A of Example 296; Compounds B, C and D of Example 296.
M+H (438).

Example 298



2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-(4-pyridinyl)-4-[2-(trifluoromethoxy)benzoyl]-1H-1,4-benzodiazepine, trihydrochloride.

Example 298 was prepared as a yellow solid from 2-(trifluoromethoxy)-benzoic acid as described for Example 297.
MS (M+H) 494.

Example 299

5 **(R)-2,3,4,5-Tetrahydro-1-[(1-methyl-1H-imidazol-5-yl)methyl]-4-(methanesulfonyl)-7-phenyl-3-(phenylmethyl)-1,4-benzodiazepine**

A. (R)-2,3,4,5-Tetrahydro-4-(methanesulfonyl)-7-phenyl-3-(phenylmethyl)-1,4-benzodiazepine

10 Mesyl chloride (0.12 ml, 1.6 mmol) was added dropwise to a solution of Compound D of Example 226 (0.50 g, 1.3 mmol) and DIEA (0.78 ml, 4.5 mmol) in methylene chloride (20 ml) at -78°C. The mixture was allowed to warm to room temperature and stirred for 16h, quenched with 10% NaHCO₃ (100 ml) and extracted with ethyl acetate (3X150 ml). The combined organic layers were dried (Na₂SO₄), filtered and concentrated under vacuum. The residue was purified by flash chromatography (5/2 hexane/ethyl acetate) to afford Compound A (0.52 g, 100%) as a yellow solid.

20 **B. 1-[1,1-Dimethylethoxycarbonyl]-4-imidazolecarboxaldehyde**

25 Di-tert-butyl dicarbonate (55.4 g, 254 mmol) was added to a suspension of 4-formyl imidazole (20.0 g, 208 mmol) and DIEA (36.2 ml, 208 mmol) in 400 ml of methylene chloride at room temperature. The mixture was heated to 40°C upon which it became a clear solution and was stirred 16 h, cooled to room temperature, quenched with saturated NaHCO₃ (200 ml) and extracted with CH₂Cl₂ (3x400 ml). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated under vacuum. The residue

was purified by flash chromatography (5-50% ethyl acetate/hexane) to afford Compound B (35.2 g, 87 %) as a white solid. MS: $(M+NH_4+CH_3CN)^+$ 256

C. 1-Methyl-5-imidazolecarboxaldehyde

5 Methyl triflate (22.3 ml, 197 mmol) was added slowly to a solution of Compound B (35.1 g, 179 mmol) in CH_2Cl_2 (740 ml) at $-78^\circ C$. The mixture was allowed to warm to room temperature slowly and stirred 16h. The resultant white precipitate was quenched portionwise with a saturated solution of potassium carbonate (112 g/100 ml H_2O) at room temperature.
10 The biphasic solution was stirred at room temperature for 30 minutes. The phases were separated and the aqueous layer was extracted with 9/1 CH_2Cl_2 / iPrOH (4X300 ml). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under vacuum. The residue was purified by flash chromatography (19/1 $CHCl_3$ /MeOH) to afford Compound C (17.4 g, 88%) as a white solid. MS $(M+H)^+$ 111
15

D. (R)-2,3,4,5-Tetrahydro-1-[(1-methyl-1H-imidazol-5-yl)methyl]-4-(methylsulfonyl)-7-phenyl-3-(phenylmethyl)-1H-1,4-benzodiazepine

20 Compound C (0.065 g, 0.59 mmol) was added to a solution of Compound A (0.23 g, 0.59 mmol) and 3A molecular sieves in 1/1 DCE: acetic acid (4 ml) and the mixture was stirred at $70^\circ C$ for 1h. Sodium triacetoxyborohydride (0.13 g, 0.59 mmol) was added and the mixture was stirred at $70^\circ C$ for 30 minutes. The latter procedure was repeated two more
25 times. The mixture was cooled to room temperature, diluted with methylene chloride (10 ml), filtered and the filtrate was concentrated under vacuum. The residue was diluted with 25% NH_4OH (100 ml) and stirred at room temperature for 10 minutes. The solution was extracted with CH_2Cl_2 (3X100 ml), the combined organic extracts were dried (Na_2SO_4), filtered and
30 concentrated under vacuum. The residue was purified by preparative HPLC (10-90% aq MeOH with 0.1% TFA) and the appropriate fractions were pooled and concentrated under vacuum. The residue was evaporated from CH_3OH (5 ml) and 1N HCl (3 ml) four times. The residue was dissolved in CH_3CN (3 ml) and water (3 ml) and lyophilized to afford Example 299 (0.26
35 g, 80 %) as a white solid. mp: $106-114^\circ C$
MS $(M+H)^+$ 487
[α] $_D^{25} = +91^\circ$ (c = 0.35, CH_3OH)

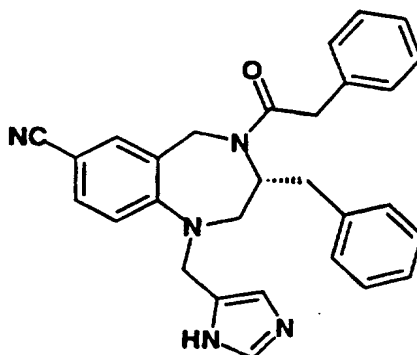
Elemental analysis for $C_{28}H_{30}N_4O_2S \cdot HCl \cdot 0.9 H_2O$

Calc: C, 57.88; H, 5.17; N, 9.06; Cl, 4.59; S, 5.18

Found: C, 57.88; H, 5.49; N, 9.14; Cl, 4.64; S, 5.31

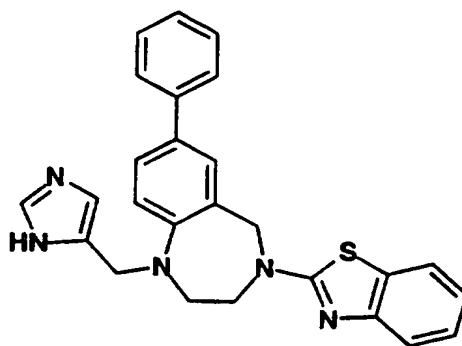
5

Example 300



10 **(R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(phenylacetyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.**

To a refluxing solution of (R)-7-cyano-2,3,4,5-tetrahydro-4-(phenylacetyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine (prepared from Compound C of Example 248 by EDC/HOAt coupling with phenylacetic acid, 0.100 g, 0.26 mmol) and 4-formylimidazole (0.025 g, 0.26 mmol) in AcOH (0.3 mL) and dichloroethane (0.5 mL) with 3A sieves was added sodium triacetoxyborohydride (0.055 g, 0.26 mmol). The mixture was stirred 16 hr, and then for 3 days, with additional aldehyde and sodium triacetoxyborohydride (3 x 1 eq each) added each day. The mixture was diluted with $CHCl_3$ (10 mL), NH_4OH (5 mL) and $NaHCO_3$ (5 mL), and stirred for 30 min. The layers were separated and the aqueous layer was extracted with $CHCl_3$ (2 x 20 mL). The combined organic extracts were washed with $NaHCO_3$, water and brine, dried over $MgSO_4$, filtered and concentrated. The product was purified by preparative HPLC (gradient of 20-90% aqueous methanol with 1% TFA) and the HCl salt formed to afford Example 300 as a light yellow solid (4 mg, 3%).
MS $(M+H)^+ = 462^+$

Exempl 301

5 **4-(2-Benzothiazolyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride.**

A. 4-(2-Benzothiazolyl)-2,3,4,5-tetrahydro-7-phenyl-1H-1,4-benzodiazepine

10 Chlorobenzothiazole (0.41 mmol, 53 mL) was added to a solution of Compound B of Example 12 (0.34 mmol, 100 mg) and triethylamine (1.36 mmol, 190 mL) in DMF (1.0 mL) and the reaction was maintained at 60°C. After 1 hr, additional 2-chlorobenzothiazole (60 mL) was added. After 2 hrs, the reaction was quenched with 2N NaOH (10 mL), extracted (2x10 mL) with CH₂Cl₂, dried over Na₂SO₄ and concentrated to afford Compound A.

15

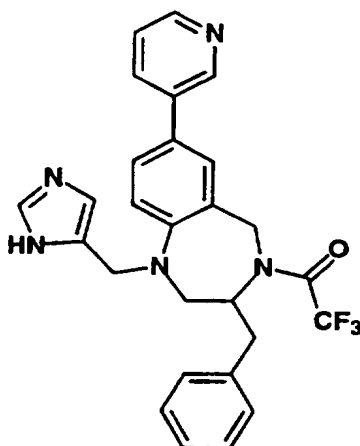
B. 4-(2-Benzothiazolyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride

20 4-Formylimidazole (0.68 mmol, 65 mg) and NaBH(OAc)₃ (0.51 mmol, 108 mg) was added to a solution of Compound A in 1:1 AcOH/(CH₂Cl)₂ (2 mL). The mixture was stirred for 1 hr, quenched with 5 mL sat'd NaHCO₃, diluted with 2N NaOH (50 mL) and extracted (2X25 mL) with 10% IPA/CH₂Cl₂. The combined organic extracts were dried over Na₂SO₄, evaporated and the residue purified by flash chromatography (94 mg, 50% yield in two steps). Lyophilization from 1N HCl afforded Example 301 as a

25

gray solid.

MS (M+H)⁺ 438

Example 302

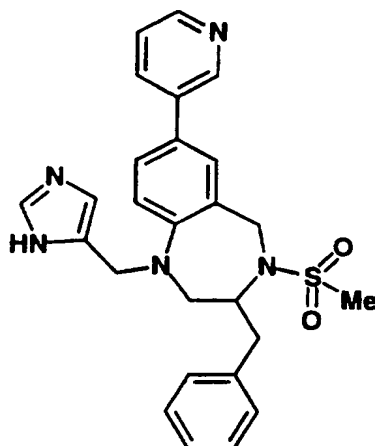
5 **2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-7-(3-pyridinyl)-4-(trifluoroacetyl)-1H-1,4-benzodiazepine, trihydrochloride.**

A. 2,3,4,5-Tetrahydro-3-(phenylmethyl)-7-bromo-1,4-bis(trifluoroacetyl)-1H-1,4-benzodiazepine

10 (CF₃CO)₂O (7.25 mmol, 1.0 mL) was added to Compound B of Example 75 (1.61 mmol, 510 mg) and triethylamine (9.66 mmol, 1.35 mL) in CH₂Cl₂ (10 mL) at RT. After 30 minutes, the reaction was concentrated and purified by flash chromatography to provide Compound A as a white solid (770 mg, 94%). MS (M-H)⁺ 507.

15 **B. 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-7-(3-pyridinyl)-4-(trifluoroacetyl)-1H-1,4-benzodiazepine, trihydrochloride**

20 Example 302 was prepared as a yellow solid from Compound A by the following sequence: Compound B of Example 296, using 3-tributylstannylpyridine; Compound C of Example 296; Compound D of Example 296.
MS (M+H)⁺ 492.

Example 303

2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methanesulfonyl)-3-(phenylmethyl)-7-(3-pyridinyl)-1H-1,4-benzodiazepine, trihydrochloride.

A. 2,3,4,5-Tetrahydro-3-(phenylmethyl)-7-(3-pyridinyl)-1H-1,4-benzodiazepine

Solid KOH (150 mg) was added to a solution of 2,3,4,5-tetrahydro-3-(phenylmethyl)-7-(3-pyridinyl)-1,4-bis(trifluoroacetyl)-1H-1,4-benzodiazepine (prepared as described in Compound B of Example 302; 100 mg, 0.2 mmol) in MeOH (4 mL). The solution was stirred at 50°C for 3 hrs, concentrated, diluted in 2N NaOH (15 mL), and extracted (3X5 mL) with 10% IPA/CH₂Cl₂ to afford 60 mg of Compound A.

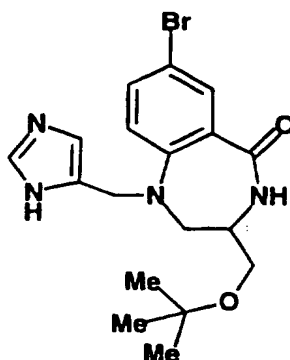
B. 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methanesulfonyl)-3-(phenylmethyl)-7-(3-pyridinyl)-1H-1,4-benzodiazepine, trihydrochloride

Methanesulfonyl chloride (0.39 mmol, 30 mL) was added to a mixture of Compound A (0.086 mmol, 27 mg) and DIEA (0.86 mmol, 150 mL) in CH₂Cl₂ (1.0 mL). The mixture was stirred for 1 hour, concentrated, diluted in 2N NaOH (10 mL) and extracted (2X5 mL) with 10% IPA/CH₂Cl₂. The solution was dried over Na₂SO₄ and concentrated. The residue was dissolved in 1:1 AcOH:(CH₂Cl₂)₂ (2 mL). 4-Formylimidazole (0.69 mmol, 66.3 mg) and NaBH(OAc)₃ (0.69 mmol, 146 mg) were added and the mixture was heated at 50°C for 16 hrs, concentrated, diluted in 2N NaOH (20 mL)/sat'd NH₄OH (5mL) and extracted (2X5 mL) with 10% IPA/CH₂Cl₂. The combined

organic extracts were concentrated and purified by prep HPLC (gradient of aqueous methanol with 0.1%TFA). Appropriate fractions were pooled, evaporated and the TFA salt was converted to the HCl salt with 1N HCl to afford Example 303 as a yellow solid (5 mg, yield in 3 steps: 9%).

5 MS (M+H)⁺ 474

Example 304



10 **7-Bromo-3-[(1,1-dimethylethoxy)methyl]-1,2,3,4-tetrahydro-1-(1H-imidazol-4-ylmethyl)-5H-1,4-benzodiazepin-5-one.**

A. 2-[(2-(fluorenylmethoxycarbonylamino)-3-(1,1-dimethylethoxy)propyl)amino]-5-bromo-benzoic acid

15 A solution of D,L-Fmoc-(O-tBu)-serinal (prepared by LAH reduction of D,L-Fmoc-Ser(tBu)-N(Me)OMe; 18 g, 49 mmol), bromoanthranilic acid (19g, 88 mmol) and glacial acetic acid (2 mL) in dry methanol (5 mL) and THF (40 mL) was stirred for 10 minutes followed by the addition of NaBH₃CN (5.5 g, 88 mmol) over 1 hour. Stirring was continued for 1 h. The
20 precipitated product was filtered, washed with water and dried under high vacuum to give 25g (89.4%) of Compound A as a white solid. (M+H)⁺ 569.

B. 7-Bromo-3-[(1,1-dimethylethoxy)methyl]-1,2,3,4-tetrahydro-5H-1,4-benzodiazepin-5-one

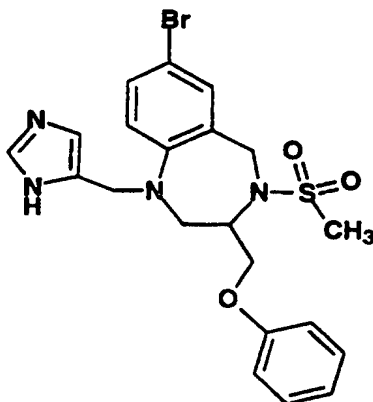
25 To a solution of Compound A (17g, 29 mmol) in THF (150 mL) was added diethylamine (30 mL, 290 mmol). The solution stirred for 2 h and concentrated. The resulting residue was dissolved in ethyl ether (100 mL) and 1N aqueous hydrogen chloride (400 mL). A heavy white precipitate formed and was filtered, washed with hexanes/ethyl ether and dried under
30 high vacuum. A portion of the resulting white solid (8.2 g, 24 mmol) with

EDC (4.5 g, 24 mmol), HOBt (3.2 g, 24 mmol) and DIEA (12.4 mL, 71 mmol) in DMF (80 mL) was stirred for 16 h and poured into a solution of 10% aq LiCl (200 mL) and ethyl acetate (90 mL). The layers were separated. The organic layer was washed with 4x 40 mL 10% aq LiCl, 4x 1N aq hydrogen chloride, 2x 50 mL brine and 1x 50 mL water. The solution was dried (Na₂SO₄), filtered and concentrated to give 7.2g (83% overall for the two steps) of Compound B as a white solid. (M+H)⁺ 329.

C. 7-Bromo-3-[(1,1-dimethylethoxy)methyl]-1,2,3,4-tetrahydro-1-(1H-imidazol-4-ylmethyl)-5H-1,4-benzodiazepin-5-one

Example 304 was prepared as a white solid in 40% yield from Compound B as described for Compound D of Example 224 (M+H)⁺ 409.

Example 305



7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(phoxymethyl)-1H-1,4-benzodiazepine, dihydrochloride.

A. 7-Bromo-3-[(1,1-dimethylethoxy)methyl]-1,2,3,4-tetrahydro-5H-1,4-benzodiazepine

Compound B of Example 304 (0.5g, 1.5 mmol) was combined with 10 mL THF and 1M LAH in THF (4 mL, 4 mmol). The solution was refluxed for 16 h. Diethyl ether (40 mL) and 1 N NaOH (40 mL) were added followed by brine and the layers were separated. The organic layer was washed with

1 N aq NaOH, dried (Na₂SO₄), filtered and concentrated to give 413 mg (88%) of Compound A as a glassy solid. MS (M+H)⁺ 314.

B. 7-Bromo-3-[(1,1-dimethylthio)methyl]-4-methanesulfonyl-1,2,3,4-tetrahydro-5H-1,4-benzodiazepine

Compound B was prepared as a white solid in 71% yield from Compound A as described for Compound C of Example 224. MS (M+H-tBu)⁺ 337.

C. 7-Bromo-3-(hydroxymethyl)-4-methanesulfonyl-1,2,3,4-tetrahydro-5H-1,4-benzodiazepine

A solution of Compound B (1.1g, 2.8 mmol) in TFA (8 mL) and methylene chloride (8 mL) was stirred for 3 h and concentrated. Trituration with ethyl ether and drying under vacuum afforded 700 mg (74%) of Compound C as a white solid. MS (M+H)⁺ 337.

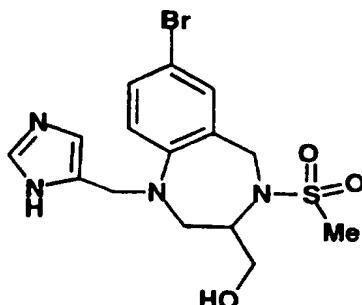
D. 7-Bromo-2,3,4,5-tetrahydro-4-(methylsulfonyl)-3-(phenoxymethyl)-1H-1,4-benzodiazepine

To a solution of Compound C (50 mg, 0.15 mmol) in methylene chloride (10 mL) was added 2,6-di-tert-butyl-4-methylpyridine (62 mg, 0.30 mmol). The solution was cooled to -40°C under N₂. Triflic anhydride (0.85 mL, 0.30 mmol) was added and the solution was stirred under N₂ for 1 h at -40°C. In a separate flask, phenol (100 mg, 1.1 mmol) was added to a solution of sodium hydride (44 mg, 1.1 mmol, 60% dispersion in mineral oil, prewashed with hexanes) in THF (2.5 mL). The solution was stirred for 20 min at ambient temperature under N₂ and was added quickly to the triflate solution. After stirring for 20 minutes, the solution was diluted with methylene chloride (40 mL) and washed with saturated aq sodium bicarbonate solution. The organic layer was dried (Na₂SO₄), filtered and concentrated to give a solid. This material was chromatographed on flash silica eluting with 1:1 ethyl acetate:hexanes to afford 30 mg (49%) of Compound D as an off-white solid. MS (M+H)⁺ 411.

E. 7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(phenoxymethyl)-1H-1,4-benzodiazepine, dihydrochloride

Example 305 was prepared from Compound D as a white solid in 27% yield as described for Compound D of Example 224.
MS (M+H)⁺ 491.

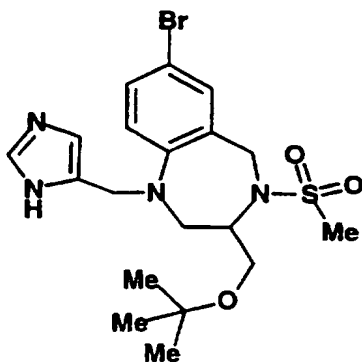
Example 306



7-Bromo-2,3,4,5-tetrahydro-3-(hydroxymethyl)-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-1H-1,4-benzodiazepine, monohydrochloride.

Example 306 was prepared as an offwhite solid in 12% yield from Compound C of Example 305 as described for Compound D of Example 224.
MS (M+H)⁺ 417.

Example 307



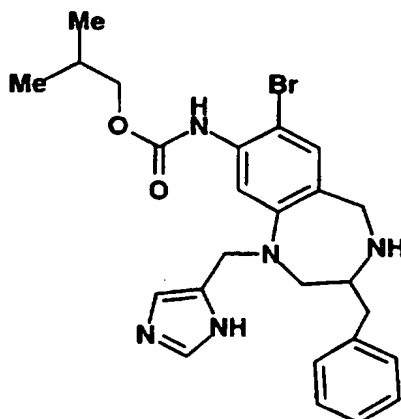
7-Bromo-3-[(1,1-dimethylethoxy)methyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-1H-1,4-benzodiazepine.

Example 307 was prepared as an offwhite solid in 23% yield from Compound B of Example 305 as described for Compound D of Example 224.

MS (M+H)⁺ 472.

5

Example 308



10 **[7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepin-8-yl]carbamic acid, 2-methylpropyl ester, trihydrochloride.**

A. 2,3,4,5-Tetrahydro-3-(phenylmethyl)-4-[(1,1-dimethylethoxy)-carbonyl]-8-amino-1H-1,4-benzodiazepine

15 A solution of 2,3,4,5-tetrahydro-3-(phenylmethyl)-8-amino-1H-1,4-benzodiazepine (described in Compound B of Example 98, 1.0 g, 3.5 mmol) and Boc anhydride (0.77g, 3.5 mmol) were stirred in THF (15 mL) under argon at RT. After 16 hrs, the mixture was concentrated. The residue was triturated with hexane and CHCl₃ to afford an olive grey solid. The filtrate
20 was concentrated and triturated with hexane and CHCl₃ to afford additional olive green solid. The solids were combined and purified by flash silica gel chromatography (20% then 30% EtOAc in hexane) to afford Compound A (0.542 g, 40%). MS (M+H)⁺ 354⁺.

25 **B. [2,3,4,5-Tetrahydro-3-(phenylmethyl)-4-[(1,1-dimethylethoxy)-carbonyl]-1H-1,4-benzodiazepin-8-yl]carbamic acid, 2-methylpropyl ester**

To a solution of Compound A (115 mg, 0.3 mol) in dichloromethane (2 mL) under argon was added DIPEA (0.1 mL, 0.6 mmol) and isobutyl

chloroformate dropwise. After 20 min, water (2 mL) and saturated NaHCO_3 were added and the mixture was extracted with chloroform (15 mL). The organic layer was dried (MgSO_4) and concentrated in vacuo to afford a solid which was purified by flash silica gel eluting with 20% EtOAc in hexanes to afford Compound B (125 mg, 92%) as a solid. MS $(\text{M}+\text{H})^+ = 454^+$

C. [7-Bromo-2,3,4,5-tetrahydro-3-(phenylmethyl)-4-[(1,1-dimethylethoxy)-carbonyl]-1H-1,4-benzodiazepin-8-yl]carbamic acid, 2-methylpropyl ester

To a solution of Compound B (100 mg, 0.22 mmol) in chloroform (2 mL) was added dropwise a solution of tetrabutylammonium tribromide (106 mg, 0.22 mmol) in chloroform (1 mL) over 5 min. After 10 min, the mixture was washed with sodium bisulfate solution (5 mL), dried (MgSO_4) and concentrated. Purification by silica gel column chromatography eluting with 20% EtOAc in hexanes afforded Compound C (110 mg, 94%) as a solid. MS $(\text{M}+\text{H})^+ = 532^+$

D. [7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-[(1,1-dimethylethoxy)-carbonyl]-1H-1,4-benzo-diazepin-8-yl]carbamic acid, 2-methylpropyl ester

To a solution of Compound C (100 mg, 0.19 mmol) and 4-formylimidazole (36 mg, 0.3 mmol) in a mixture of dichloromethane (2 mL) and acetic acid (0.6 mL) was added 3A molecular sieves and the mixture was stirred for 15 min. Sodium triacetoxyborohydride (105 mg, 0.5 mmol) was added and the mixture was stirred overnight (18 hr). Another portion of the aldehyde and borohydride reagent (36 mg and 105 mg respectively) were added. After 4 hr., the mixture was filtered through celite and washed with chloroform. The filtrate was concentrated and treated with chloroform and NH_4OH (10 mL each). After stirring vigorously for 30 min, the organic layer was separated, dried (MgSO_4), and concentrated in vacuo to afford Compound D (110 mg, 86%). MS $(\text{M}+\text{H})^+ = 612^+$

E. [7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepin-8-yl]carbamic acid, 2-methyl-propyl ester, trihydrochloride

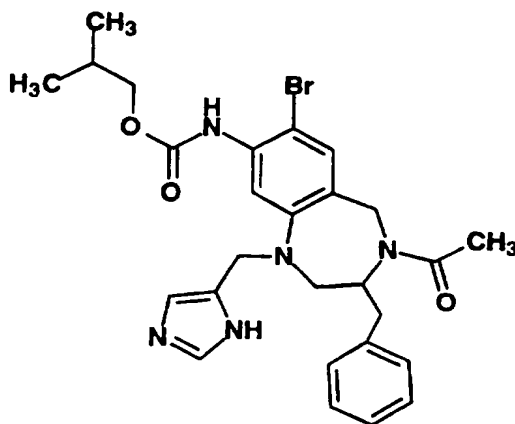
To a solution of Compound D (105 mg, 0.17 mmol) in chloroform (1 mL) was added HCl in dioxane (3 mL, 4M solution). After 4 hr the mixture

was concentrated. Chloroform (5 mL) was added and the mixture concentrated in vacuo to afford Example 308 as an off-white powder (110 mg, 100%).

MS (M+H)⁺ = 512

5

Example 309

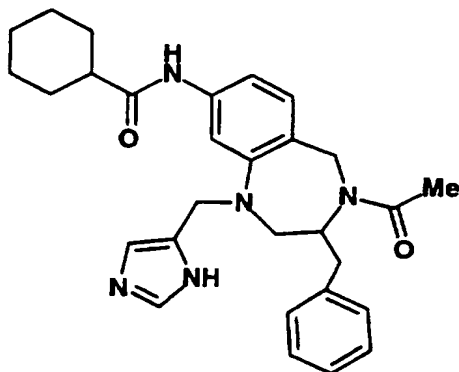


10 **[4-Acetyl-7-bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepin-8-yl]carbamic acid, 2-methyl-propyl ester.**

To a solution of Example 308 (18 mg, 0.03 mmol) in DMF (0.2 mL) were added pyridine (0.3 mL), acetic anhydride (0.2 mL), and DMAP (10 mg) and the mixture was stirred for 20 hr. Acetic anhydride (0.1 mL) was added and the mixture was stirred for 4 hr. The mixture was partitioned between chloroform and water (10 mL each). The organic layer was separated and washed with saturated CuSO₄ (2x10 mL), dried (K₂CO₃) and concentrated. Purification by RP HPLC eluting with 40-90% aqueous methanol containing 0.1% TFA on a C-18 column afforded a solid which was treated with 1N aqueous HCl (2x10 mL) followed by concentration. The solid was dissolved in water and lyophilized to afford Example 309 as a pale yellow solid (13 mg, 70%).

20 MS (M+H)⁺ = 554

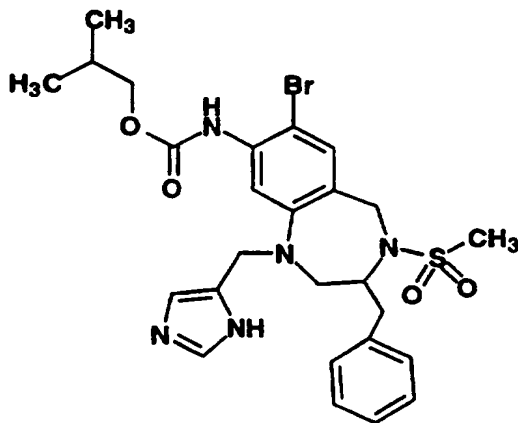
25

Example 310

5 **N-[4-Acetyl-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepin-8-yl]cyclohexanecarboxamide, dihydrochloride.**

Example 310 was prepared in 50% yield as a pale yellow solid from Compound C of Example 246 as described for Example 309.

10 MS (M+H)⁺ = 486

Example 311

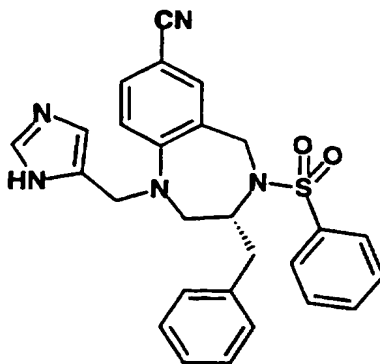
15 **[7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepin-8-yl]carbamic acid, 2-methylpropyl ester.**

20 To a solution of Example 308 (31 mg, 0.05 mmol) in DMF (0.2 mL) at RT were added TEA (0.2 mL), dichloromethane (0.2 mL), and methanesulfonyl chloride (0.024 mL, 0.3 mmol) and the mixture was stirred

for 18 hr and partitioned between chloroform and saturated NaHCO₃ (10 mL each). The organic layer was separated, dried (K₂CO₃) and concentrated. Purification by RP HPLC eluting with 40-90% aqueous methanol containing 0.1% TFA on a C-18 column afforded a solid which was treated with 1N aqueous HCl (2x10 mL) followed by concentration. The solid was dissolved in water and lyophilized to afford Example 311 as a pale yellow solid (13 mg, 70%).

MS (M+H)⁺ = 590

Example 312



(R)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(phenylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine-7-carbonitrile, monohydrochloride.

A. (R)-2,3,4,5-Tetrahydro-4-(phenylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine-7-carbonitrile

To a stirred and chilled (0°, ice bath) solution of Compound C of Example 248 (45g, 171.54mmole) containing DIEA (50 ml, 287 mmol) in anhydrous CH₂Cl₂ (1 L) under argon was added dropwise a solution of benzenesulfonyl chloride (30 ml, 235 mmol) in anhydrous CH₂Cl₂ (50ml). After the addition was complete, the mixture was warmed to room temperature and stirred for 4 hr. The solution was diluted with CH₂Cl₂ (500ml), washed with water (2x250ml), 10% KHSO₄ (750ml), saturated NaHCO₃ and brine, which was crystallized from EtOAc-hexane to give 65g (94%) of Compound A as solid. MS (M-H)⁻ 402.

¹³C-NMR (CDCl₃) 40.22, 46.00, 47.23, 61.36, 116.34, 119.55, 120.99, 126.99, 127.11, 128.10, 129.76, 129.40, 131.97, 132.09, 134.03, 136.77, 139.53, 150.77ppm

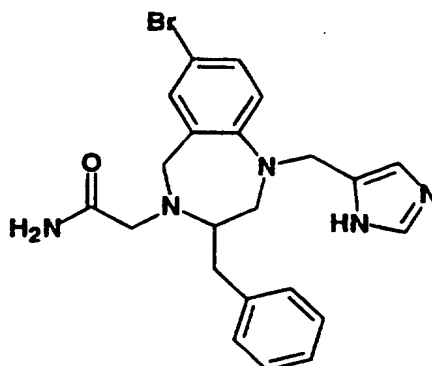
B. (R)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(phenylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine-7-carbonitrile, monohydrochloride

5 To a stirred solution of Compound A (64.3 g, 159 mmol) and 4-formylimidazole (15.3 g, 159 mmol) in a mixture of HOAc (glacial, 150 ml) and 1,2-dichloroethane (720 ml) under argon was added sodium triacetoxyborohydride (33.8 g, 159 mmol). The mixture was heated to 60°C for 6 hr. Additional 4-formylimidazole (15.3g) and sodium
10 triacetoxyborohydride (33.8g) were added. The addition was repeated three times until HPLC showed 7% unreacted Compound A. The resulting solution was cooled to room temperature. MeOH (250ml) was slowly added and the mixture was stirred for 30 minutes and evaporated. The residue was azeotroped with toluene (2x500ml). The gummy residue was diluted with
15 saturated NaHCO₃ solution and stirred. Solid NaHCO₃ was added until the foaming ceased. The slurry was extracted with EtOAc (3x1L). The combined EtOAc extracts were washed with saturated NaHCO₃ solution and brine, dried over anhydrous MgSO₄ and evaporated to give a foam. This was flash-chromatographed on a column of silica gel (E. Merck 230-400 mesh,
20 1.6 kg) eluting with EtOAc-MeOH (95:5) to give the free base of Example 312. This was dissolved in EtOAc (1.0L), treated with a solution of 1.0N HCl in Et₂O (250 ml), and the mixture stirred for 30 minutes and filtered. The solid was washed with EtOAc (500ml) and Et₂O (500ml) and dried in high vacuum at 50° overnight to give 58 g (70%) of Example 312 as a solid.
25 MS (M+ H)⁺ = 484
Analysis calculated for C₂₇H₂₅N₅O₂S • 0.7 H₂O • 1 HCl • 0.05 EtOAc • 0.03 ether.

Calc'd: C, 60.85; H, 5.25; N, 12.99; Cl, 6.57; S, 5.94.

Found: C, 60.85; H, 5.19; N, 13.05; Cl, 6.60; S, 5.95.

30

Example 313

5 **7-Bromo-1,2,3,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4H-1,4-benzodiazepine-4-acetamide.**

A. 7-Bromo-1,2,3,5-tetrahydro-3-(phenylmethyl)-4H-1,4-benzodiazepine-4-acetamide

10 A mixture of Compound B of Example 75 (250 mg, 0.74 mmol), DIEA (0.067 mL, 0.74 mmol) and 2-chloroacetamide (69 mg, 0.74 mmol) in THF (10 mL) was stirred under argon at room temperature for 8 hours. The mixture was partitioned in brine (50 mL) and ethyl acetate (50 mL), the aqueous layer was extracted with ethyl acetate (2 x 50 mL), and the combined organic layers were dried (MgSO₄) and concentrated to provide
15 Compound A as a clear oil (260 mg, 94 %).

B. 7-Bromo-1,2,3,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4H-1,4-benzodiazepine-4-acetamide

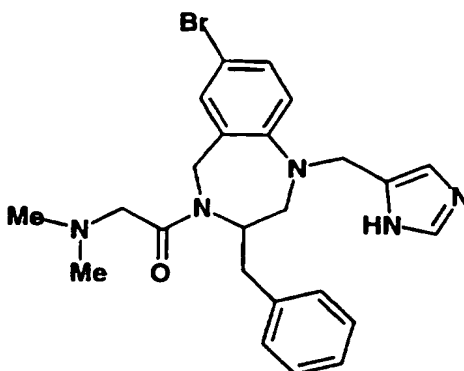
20 Example 313 was prepared as a white solid in 38% yield from Compound A as described in Compound D of Example 1, with stirring for 18 hours and purification by preparative HPLC.

MS (M+ H)⁺ = 454

Analysis calculated for C₂₂H₂₄N₅OBr • 0.3 H₂O • 1.5 TFA.

Calc'd: C, 45.81; H, 3.95; N, 10.35; Br, 11.81; F, 16.01.

25 Found: C, 45.43; H, 3.80; N, 9.96; Br, 11.50; F, 15.74.

Example 314

5 **7-Bromo-4-[(dimethylamino)acetyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine.**

A. 7-Bromo-4-(bromoacetyl)-2,3,4,5-tetrahydro-3-(phenylmethyl)-1H-1,4-benzodiazepine

10 Compound A was prepared as a clear oil from Compound B of Example 75 and bromoacetyl bromide as described for Compound A of Example 313, with purification by using flash chromatography (silica, 3:1 hexanes: ethyl acetate)

15 **B. 7-Bromo-4-[(dimethylamino)acetyl]-2,3,4,5-tetrahydro-3-(phenylmethyl)-1H-1,4-benzodiazepine**

To a solution of Compound A (126 mg, 0.29 mmol) in THF (2 mL) was added dimethyl amine (2 mL, 1 M in THF). The solution was stirred at room temperature in a sealed pressure tube for 7 hours, poured into water and extracted with ethyl acetate. The solution was dried (MgSO_4) and
20 concentrated to afford Compound B as an oil (110 mg, 94 %).

C. 7-Bromo-4-[(dimethylamino)acetyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine

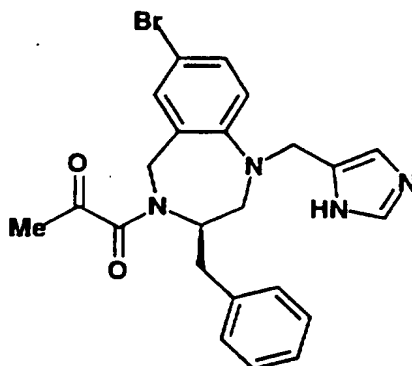
25 Compound C was prepared as a white solid in 65% yield from Compound B as described for Compound B of Example 313.

MS ($\text{M} + \text{H}$)⁺ = 483

Analysis calculated for $\text{C}_{24}\text{H}_{28}\text{N}_5\text{OBr} \cdot 1.2 \text{ H}_2\text{O} \cdot 2.1 \text{ TFA}$.

Calc'd: C, 45.56; H, 4.41; N, 9.42; Br, 10.75; F, 16.10.

30 Found: C, 45.75; H, 4.02; N, 9.19; Br, 11.14; F, 16.08.

Example 315

- 5 **(R)-7-Bromo-4-(1,2-dioxopropyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate.**

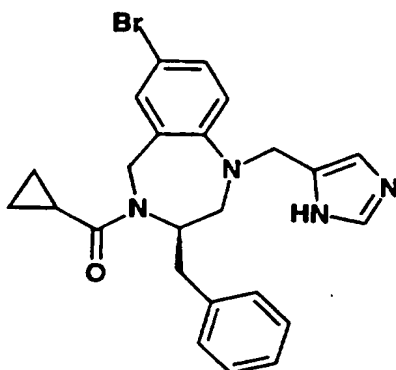
10 Example 315 was prepared as a white solid in 25% overall yield from Compound B of Example 224 by an EDC/HOBt mediated coupling of pyruvic acid in DMF, with purification by flash chromatography (silica, 4:1 hexanes: ethyl acetate), followed by the method of Compound B of Example 313.

MS (M+ H)⁺ = 468

- 15 Analysis calculated for C₂₃H₂₃N₄O₂Br • 0.8 H₂O • 0.95 TFA.

Calc'd: C, 50.68; H, 4.36; N, 9.49; Br, 13.54; F, 9.18.

Found: C, 50.37; H, 4.04; N, 9.23; Br, 14.07; F, 9.55.

Exempl 316

5 **(R)-7-Bromo-4-(cyclopropylcarbonyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate.**

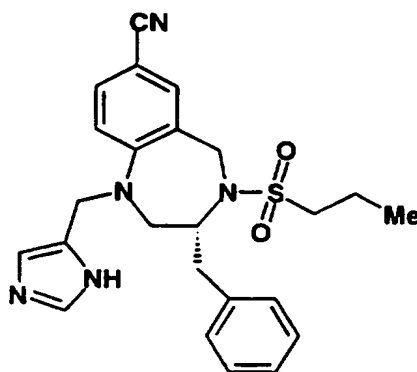
10 Example 316 was prepared as a white solid in 6% overall yield from Compound B of Example 224 and cyclopropanecarboxylic acid by the two step procedure described in Example 315, with no purification of the intermediate.

MS (M+ H)⁺ = 466

Analysis calculated for C₂₄H₂₅N₄OBr • 1.0 H₂O • 0.8 TFA.

Calc'd: C, 52.59; H, 4.68; N, 9.43; Br, 13.46; F, 9.60.

15 Found: C, 52.62; H, 4.37; N, 9.46; Br, 12.23; F, 9.46.

Example 317

20 **(R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(propylsulfonyl)-1H-1,4-benzodiazepine, monohydrochloride.**

A. (R)-7-Cyano-2,3,4,5-tetrahydro-3-(phenylmethyl)-4-(propylsulfonyl)-1H-1,4-benzodiazepine

n-Propylsulfonylchloride (3.4 ml, 34 mmol) was added dropwise to a solution of Compound C of Example 248 (6.0 g, 23 mmol) and DIEA (12 ml, 68 mmol) in methylene chloride (120 ml) at -78°C. The mixture was allowed to warm to room temperature and stirred for 16h, quenched with 10% NaHCO₃ (50 ml) and extracted with methylene chloride (3X75 ml). The combined organic layers were dried (Na₂SO₄), filtered and concentrated under vacuum. The residue was purified by flash chromatography (2/1 hexane/ethyl acetate) to afford Compound A (7.1 g, 85%) as a yellow solid. MS (M+H)⁺ 370

Analysis calculated for C₂₀H₂₃N₃O₂S • 0.19 H₂O.

Calc'd: C, 64.42; H, 6.32; N, 11.27.

Found: C, 64.43; H, 6.25; N, 11.09.

B. (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(propylsulfonyl)-1H-1,4-benzodiazepine, monohydrochloride

4-Formylimidazole (3.1 g, 33 mmol) was added to a solution of Compound A (6.0 g, 16 mmol) and 3A molecular sieves in 1/1 CH₂Cl₂:acetic acid (80 ml) and the mixture was stirred at 70°C for 1h. Sodium triacetoxyborohydride (6.9 g, 33 mmol) was added and the mixture was stirred at 70°C for 30 minutes. 4-Formylimidazole (3.1 g, 33 mmol, 2.0 equiv) was again added to the mixture and stirring was continued at 70°C for 1h. Sodium triacetoxyborohydride (6.9 g, 33 mmol, 2.0 equiv) was added and the mixture was stirred at 70°C for 30 minutes. Addition of more formylimidazole and hydride was repeated eight times. The mixture was cooled to room temperature, diluted with methylene chloride (200 ml), filtered and the filtrate concentrated under vacuum. The residue was diluted with 25% NH₄OH (200 ml). The solution was stirred at room temperature for 10 minutes, extracted with CH₂Cl₂ (2X200 ml) and the combined organic extracts were dried (MgSO₄), filtered and concentrated. The residue was purified by preparative HPLC (gradient of aq MeOH with 0.1% TFA) and the appropriate fractions were isolated and concentrated under vacuum. The residue was dissolved in CH₃OH (20 ml) and 1N HCl (40 ml) and concentrated under vacuum and this procedure was repeated 3X. The

residue was dissolved in CH₃CN (20 ml) and 1N HCl (20 ml) and lyophilized to afford Example 317 (6.8 g, 74 %) as a white solid., mp: 140-151°C.

MS (M+H)⁺ 450

Analysis calculated for C₂₄H₂₇N₅O₂S • 1.1 HCl • 0.59 H₂O.

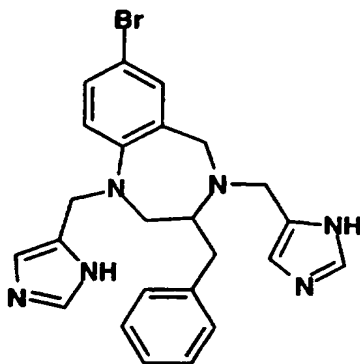
5 Calc'd: C, 57.62; H, 5.90; N, 14.00; Cl, 7.79; S, 6.41.

Found: C, 57.61; H, 5.70; N, 13.97; Cl, 7.62; S, 6.44.

[α]_D = + 201° (c = 1.41, CH₃OH)

Example 318

10

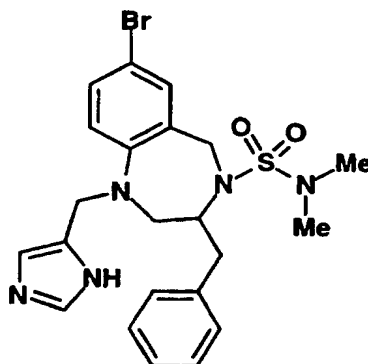


7-Bromo-2,3,4,5-tetrahydro-1,4-bis(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.

15

Example 318 was prepared in 55% yield as a white solid from Compound B of Example 75 as described for Compound D of Example 1, using 3 equivalents of formylimidazole and stirring for 2 hours.

MS (M+H)⁺ = 477

Example 319

5 **7-Bromo-1,2,3,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-N,N-dimethyl-3-(phenylmethyl)-4H-1,4-benzodiazepine-4-sulfonamide, monohydrochloride.**

A. 7-Bromo-1,2,3,5-tetrahydro-N,N-dimethyl-3-(phenylmethyl)-4H-1,4-benzodiazepine-4-sulfonamide

10 A stirred solution of Compound B of Example 75 (100 mg, 0.32 mmol), N,N-dimethylsulfamoyl chloride (50 mg, 0.35 mmol) and DIPEA (61 μ L, 0.35 mmol) in acetonitrile in the presence of a catalytic amount of DMAP was heated at reflux for 18 h. The mixture was partitioned between ethyl acetate and 1 N HCl solution. The organic layer was separated, dried
15 (MgSO₄) and concentrated. The residue was purified by flash chromatography (1:2, hexanes:ethyl acetate) to give Compound A as an oil.

B. 7-Bromo-1,2,3,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-N,N-dimethyl-3-(phenylmethyl)-4H-1,4-benzodiazepine-4-sulfonamide, monohydrochloride

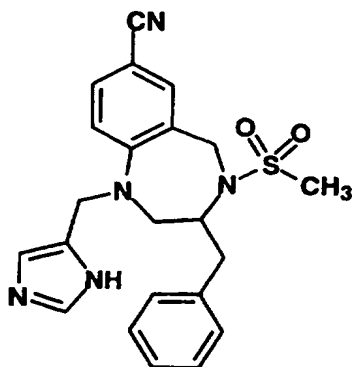
Example 319 was prepared in 92% yield as a solid from Compound A as described for Compound D of Example 224.

MS (M+H)⁺ 504

Analysis calculated for C₂₂H₂₆N₅O₂SBr • 1.0 HCl • 0.5 ether.

25 Calc'd: C, 49.88; H, 5.58; N, 12.12; Br, 13.82; S, 5.55.

Found: C, 49.90; H, 5.42; N, 12.13; Br, 13.22; S, 6.44.

Example 320

5 **2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine-7-carbonitrile, monohydrochloride.**

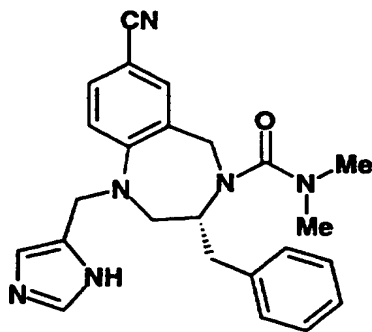
Example 320 was prepared as a yellow solid from Compound B of Example 75 as described in the following sequence: Compound C of
10 Example 224, Compound A of Example 225, and Compound B of Example 225.

MS (M+H)⁺ 422

Analysis calculated for C₂₂H₂₃N₅O₂S • 1.0 HCl • 0.2 CH₃OH.

Calc'd: C, 57.42; H, 5.38; N, 15.08; Cl, 7.63; S, 6.90.

15 Found: C, 57.12; H, 5.58; N, 11.94; Cl, 7.77; S, 4.95.

Example 321

20 **(R)-7-Cyano-1,2,3,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-N,N-dimethyl-3-(phenylmethyl)-4H-1,4-benzodiazepine-4-carboxamide, monohydrochloride.**

Example 321 was prepared as a yellow solid from Compound C of Example 248 by the following sequence: Compound A of Example 319, using dimethylcarbamoyl chloride and stirring at 60°C for 2 h and chromatography with 1:1 hexanes:ethyl acetate; Compound B of Example

225. mp: 147-150°C.

MS (M+ H)⁺ = 415

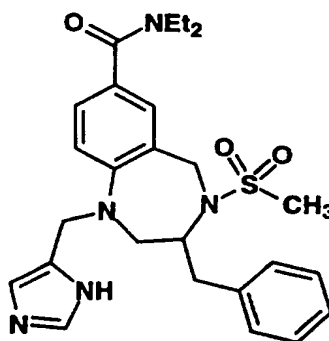
Analysis calculated for C₂₄H₂₆N₆O • 0.74 H₂O • 1.0 HCl.

Calc'd: C, 62.09; H, 6.18; N, 18.10; Cl, 7.61.

Found: C, 62.09; H, 6.04; N, 17.86; Cl, 7.91.

[α]_D²⁰: +244 ° (c = 0.24, MeOH).

Example 322



N,N-Diethyl-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methanesulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine-7-carboxamide, monohydrochloride.

A. 2,3,4,5-tetrahydro-4-(methanesulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine-7-carboxylic acid

A solution of Compound A of Example 225 (200 mg, 0.59 mmol) in ethanol in the presence of 10N NaOH solution (4 mL, 40 mmol) was heated at reflux for 5 h. The mixture was cooled to room temperature, concentrated and aqueous HCl was added to adjust the pH to 3. The mixture was concentrated. The residue was partitioned between 1N HCl and ethyl acetate. The organic layer was separated, dried over MgSO₄ and concentrated. The residue was triturated with methanol to give Compound A as a solid (156 mg, 73%).

B. N,N-Diethyl-2,3,4,5-tetrahydro-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine-7-carboxamide

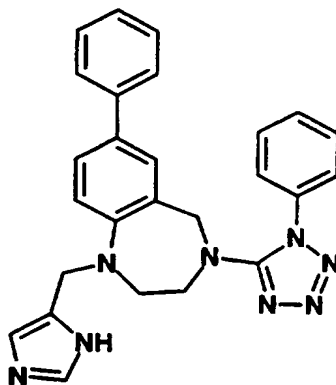
To a solution of Compound A (50 mg, 0.14 mmol) in DMF was added diethylamine (50 μ L), followed by catalytic amounts of HOBT and DMAP and then EDC (30 mg). The mixture was stirred at room temperature for 2 days and partitioned between ethyl acetate and 1 N HCl solution. The organic layer was separated, washed with sat. NaHCO_3 solution, dried MgSO_4 , concentrated to give Compound B as an oil.

C. N,N-Diethyl-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine-7-carboxamide, monohydrochloride

Compound C was prepared from Compound B as described for Compound B of Example 225.

MS $(M+H)^+ = 496$.

Example 323



2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-(1-phenyl-1H-tetrazol-5-yl)-1H-1,4-benzodiazepine, monohydrochloride.

A. 2,3,4,5-Tetrahydro-7-phenyl-4-(1-phenyl-1H-tetrazol-5-yl)-1H-1,4-benzodiazepine

A solution of Compound B of Example 12 (100 mg, 0.45 mmol) in DMF (2 mL) was treated with 5-chloro-1-phenyltetrazole (100 mg, 0.55 mmol) in the presence of potassium carbonate (60 mg). The mixture was stirred at 60°C for 18 h and partitioned between ethyl acetate and sat. NH_4Cl solution. The organic layer was washed with sat. NaHCO_3 solution, dried

(MgSO₄), and concentrated. The residue was purified by column chromatography to give Compound A as a white solid (75 mg, 45%), mp: 150-151°C.

5 **B. 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-(1-phenyl-1H-tetrazol-5-yl)-1H-1,4-benzodiazepine, monohydrochloride**

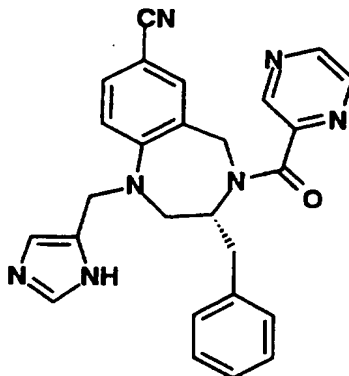
Compound B was prepared as a yellow solid from Compound A as described for Compound D of Example 1, mp 158°C.

10 Analysis calculated for C₂₆H₂₄N₈ • 0.5 CH₃OH • 2.5 HCl.

Calc'd: C, 57.28; H, 5.17; N, 20.16.

Found: C, 57.62; H, 5.12; N, 19.93.

Example 324



15
(R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(2-pyrazinylcarbonyl)-4H-1,4-benzodiazepine, monohydrochloride.

20

Example 324 was prepared as a yellow solid from Compound C of Example 248 and pyrazinecarboxylic acid by the following sequence:

Compound B of Example 322, with stirring for 18 hours and purification by flash chromatography (3:2, ethyl acetate: hexanes); Compound B of

25 Example 225.

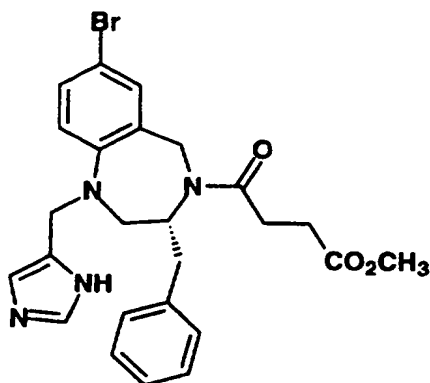
MS (M+ H)⁺ = 450.

Analysis calculated for C₂₆H₂₃N₇O • 1.2 H₂O • 1.0 HCl • 1.2 toluene.

Calc'd: C, 66.09; H, 5.78; N, 16.35; Cl, 5.91.

Found: C, 65.83; H, 5.45; N, 16.11; Cl, 5.96.

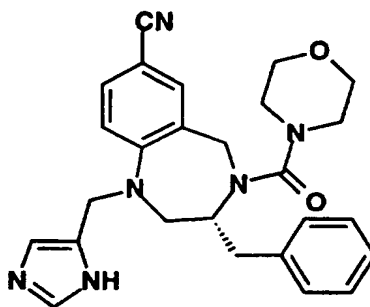
30

Example 325

5 **(R)-4-[7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4H-1,4-benzodiazepin-4-yl]-4-oxobutanoic acid, methyl ester, monohydrochloride.**

10 **A. (R)-4-[7-Bromo-2,3,4,5-tetrahydro-3-(phenylmethyl)-4H-1,4-benzodiazepin-4-yl]-4-oxobutanoic acid, methyl ester**
A stirred solution of Compound B of Example 224 (100 mg, 0.31 mmol) was treated with succinic anhydride (40 mg, 0.40 mmol) in ethyl acetate. The mixture was stirred at room temperature for 18 h and partitioned with 1N HCl solution. The organic layer was dried (MgSO₄), and concentrated to afford Compound A.

15 **B. (R)-4-[7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4H-1,4-benzodiazepin-4-yl]-4-oxobutanoic acid, methyl ester, monohydrochloride**
Compound B was prepared as a yellow solid from Compound A as described for Compound B of Example 225.
20 MS (M+ H)⁺ =511.

Example 326

5 **(R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(4-morpholinylcarbonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.**

10 Example 326 was prepared as a yellow solid from Compound C of Example 248 and morpholinocarbonyl chloride as described for Example 321.

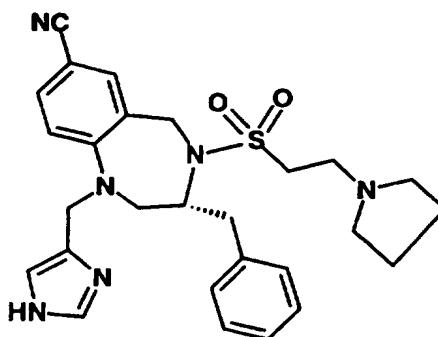
MS (M+ H)⁺ = 457.

Analysis calculated for C₂₆H₂₈N₆O₂ • 0.8 H₂O • 1.2 HCl • 0.2 ether.

Calc'd: C, 60.79; H, 6.24; N, 15.87, Cl, 8.03.

Found: C, 60.85; H, 6.02; N, 15.56; Cl, 8.06.

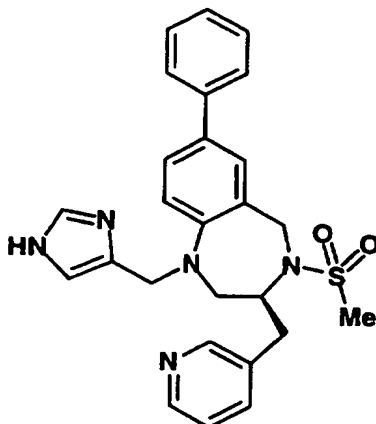
15

Example 327

20 **(R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-[[2-(1-pyrrolidinyl)ethyl]sulfonyl]-1H-1,4-benzodiazepine, dihydrochloride.**

Example 327 was prepared in 46% yield as a light yellow solid from Compound A of Example 250 and pyrrolidine as described for Compound B of Example 250.

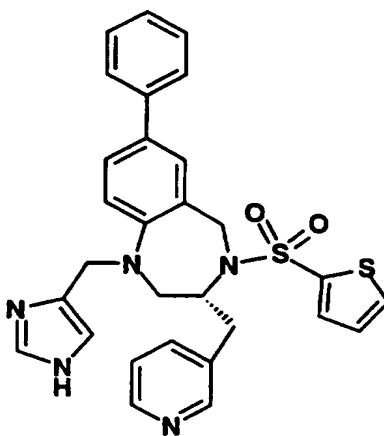
25 MS (M+ H)⁺ = 505.

Example 328

- 5 **(S)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-7-phenyl-3-(3-pyridinylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.**

10 Example 328 was prepared as an off white solid from L-(3-pyridyl)alanine and Compound B of Example 226 by the following sequence: Compound C of Example 226; Compound D of Example 226; Compound B of Example 264; Compound C of Example 264.
MS (M+H)⁺ 474.

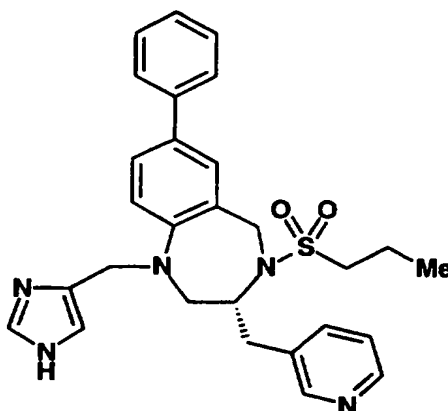
15

Example 329

- 20 **(R)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-3-(3-pyridinylmethyl)-4-(2-thienylsulfonyl)-1H-1,4-benzodiazepine, dihydrochloride.**

Example 329 was prepared as an off white solid from (R)-2,3,4,5-tetrahydro-7-phenyl-3-(3-pyridinylmethyl)-1H-1,4-benzodiazepine (prepared as described in Example 273) and 2-thiophenesulfonyl chloride by the following sequence: Compound C of Example 224; Compound D of Example 224.
MS (M+H)⁺ 542.

Example 330



(R)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-(propylsulfonyl)-3-(3-pyridinylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.

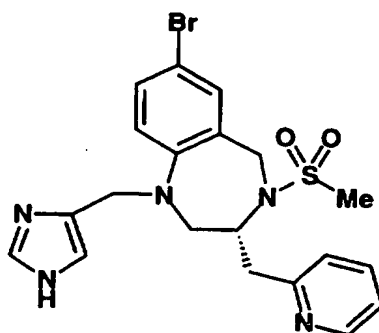
A. (R)-2,3,4,5-Tetrahydro-7-phenyl-4-(propylsulfonyl)-3-(3-pyridinylmethyl)-1H-1,4-benzodiazepine

To a stirred solution of (R)-2,3,4,5-tetrahydro-7-phenyl-3-(3-pyridinylmethyl)-1H-1,4-benzodiazepine (prepared as described in Example 273; 200 mg, 0.63 mmol) and DIEA (0.33 mL, 1.9 mmol) was added propanesulfonyl chloride (0.11 mL, 0.94 mmol) at -60°C under argon. The mixture was kept at 4°C for two days, quenched with aqueous saturated NaHCO₃ solution (10 mL) and extracted with CH₂Cl₂ (3 x 10 mL). The combined extracts were dried (Na₂SO₄) and evaporated under reduced pressure to afford Compound A as a yellow solid. MS (M+H)⁺ 422.

B. (R)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-(propylsulfonyl)-3-(3-pyridinylmethyl)-1H-1,4-benzodiazepine, monohydrochloride

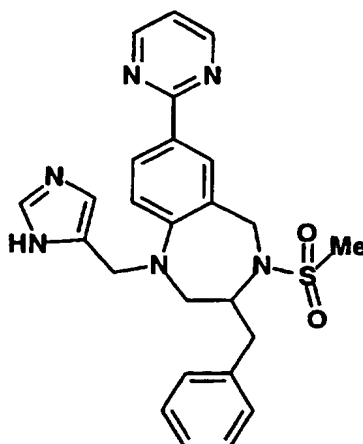
Compound B was prepared as a yellow solid from Compound A in 45% yield as described for Compound D of Example 224, with purification by preparative HPLC (gradient of aqueous methanol with 0.1% TFA). The HCl salt was prepared by adding 1N HCl in ether to a solution of the TFA salt in ethyl acetate and evaporation. MS: (M+H)⁺ 502

Example 331



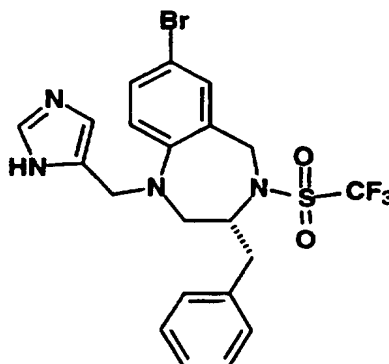
(R)-7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(2-pyridinylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.

Example 331 was prepared as a yellow solid from D-(2-pyridyl)alanine and Compound B of Example 226 using the following sequence: Compound C of Example 226; Compound D of Example 226, with refluxing for 48 hr; Compound B of Example 264, with purification by preparative HPLC using a gradient of aqueous methanol with 0.1% TFA; Compound C of Example 264.
MS (M+H)⁺ 478.

Example 332

2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-
5 (methylsulfonyl)-3-(phenylmethyl)-7-(2-pyrimidinyl)-1H-1,4-
benzodiazepine, dihydrochloride.

Example 332 was prepared as a yellow solid from Compound A of
Example 231 and 2-stannylpyrimidine as described for Compound B of
10 Example 231 and Compound C of Example 231.
MS (M+H)⁺ 475.

Example 333

15

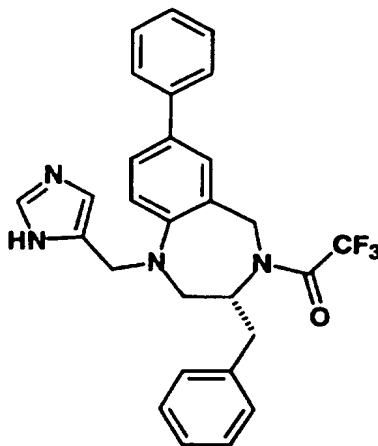
(R)-7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-
(phenylmethyl)-4-[(trifluoromethyl)sulfonyl]-1H-1,4-
20 benzodiazepine, monohydrochloride.

20

Example 333 was prepared in 44% yield as an off-white solid from Compound B of Example 224 as described for Compound C of Example 224 (using trifluoromethanesulfonyl anhydride instead of methanesulfonyl chloride) and Compound D of Example 224.

5 MS (M+H)⁺ 528.

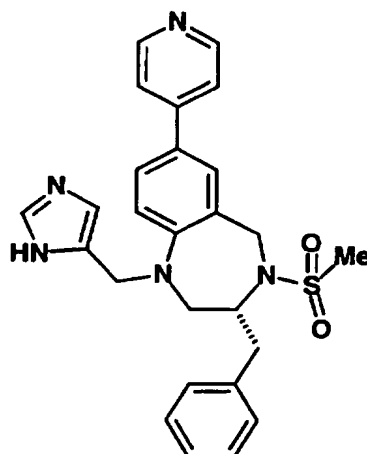
Example 334



10 **(R)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-3-(phenylmethyl)-4-(trifluoroacetyl)-1H-1,4-benzodiazepine, monohydrochloride.**

Example 334 was prepared in 26% yield as a white solid from Compound D of Example 226 by reaction with trifluoroacetic anhydride and DIEA in methylene chloride, followed by the method of Compound C of Example 264, with purification by preparative HPLC (gradient of aqueous methanol with 0.1% TFA). The HCl salt was prepared by lyophilization twice from 1N HCl.

20 MS (M+H)⁺ 491.

Exempl 335

5 **(R)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(phenylmethyl)-7-(4-pyridinyl)-1H-1,4-benzodiazepine, dihydrochloride.**

A. (R)-2,3,4,5-Tetrahydro-3-(phenylmethyl)-7-(4-pyridinyl)-1H-1,4-benzodiazepin-2,5-dione

10 A mixture of Compound A of Example 224 (55.6 mmol, 19.2g), 4-stannylpyridine (111 mmol, 40.9 g) and Pd(PPh₃)₄ (8.24 mmol, 9.6g) in toluene (2000 mL) was degassed and heated to 110°C for 16 hrs. The reaction was concentrated, diluted with 1:1 ether/hexanes and filtered. The solid was washed with 500 mL of 1:1 ether/hexanes to afford 16.7 g of
15 Compound A. The combined filtrate was concentrated and filtered to yield 5.8 g of Compound A (total yield 80%). MS (M+H)⁺ 344.

B. (R)-2,3,4,5-Tetrahydro-3-(phenylmethyl)-7-(4-pyridinyl)-1H-1,4-benzodiazepine

20 A suspension of Compound A (16.7, 32 mmol) in THF (250 mL) was treated with BH₃•THF (1.0 M in THF). The mixture was heated to reflux for 12 hrs and quenched by the slow addition of 6N HCl (500 mL). THF was removed under reduced pressure, and the remaining solution was made alkaline with the slow addition of concentrated NaOH. The aqueous phase
25 was extracted with 10%IPA-CH₂Cl₂ (3X300 mL), dried over Na₂SO₄ and concentrated to isolate 9.0 g (90% yield) of Compound B. MS (M+H)⁺ 316.

C. (R)-2,3,4,5-Tetrahydro-4-(methylsulfonyl)-3-(phenylmethyl)-7-(4-pyridinyl)-1H-1,4-benzodiazepine

To a solution of Compound B (28.5 mmol, 9.0 g) in CH₂Cl₂ (200 mL) was added TEA (142.5 mmol, 20 mL) and methanesulfonyl chloride (37.5 mmol, 2.9 mL). The mixture was stirred at rt for 1 hr, poured over 2N NaOH (500 mL) and extracted with 10%IPA-CH₂Cl₂ (3X250 mL). The combined organic layers were dried over Na₂SO₄, concentrated, and azeotroped with toluene to afford Compound C.

D. (R)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(phenylmethyl)-7-(4-pyridinyl)-1H-1,4-benzodiazepine, dihydrochloride

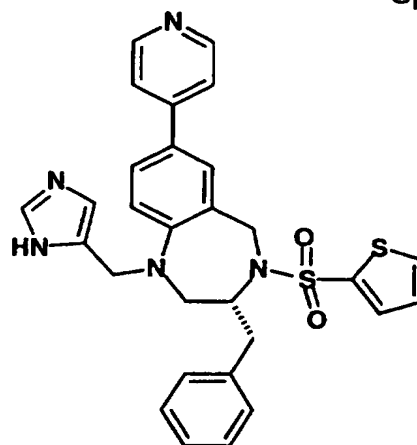
Crude Compound C was dissolved in 300 mL of 1:1 AcOH:CH₂Cl₂ together with NaBH(OAc)₃ (123 mmol, 26g) and 4-formylimidazole (123 mmol, 11.8 g) and the mixture heated to 55°C for 3 hrs. The reaction was concentrated, diluted with 2N NaOH (500 mL) and extracted with 10%IPA-CH₂Cl₂ (3X250 mL). The combined organic layers were evaporated and the residue purified by preparative HPLC (gradient of aq methanol with 0.1% TFA). The TFA salt was converted to the HCl salt with 1N HCl (2X150 mL) to afford Compound D as a yellow solid (2.9 g, 18% from Compound B). MS (M+H)⁺ 491.

Example 336-343

Examples 336-343 were prepared from the appropriate sulfonyl chloride and Compound B of Example 335 as described for Compounds C and D of Example 335 (Exs 336-338) or from Compound C of Example 248 as described for Compound A of Example 317 (from 0°C to rt) and Compound D of Example 335 (Exs 339-343).

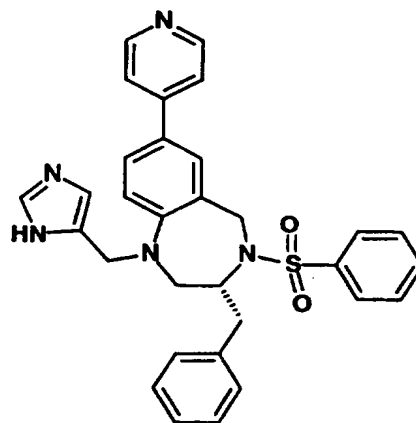
Example**Mass
Spectrum**

336 (R)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-7-(4-pyridinyl)-4-(2-thienylsulfonyl)-1H-1,4-benzodiazepine, dihydrochloride. BMS-218962



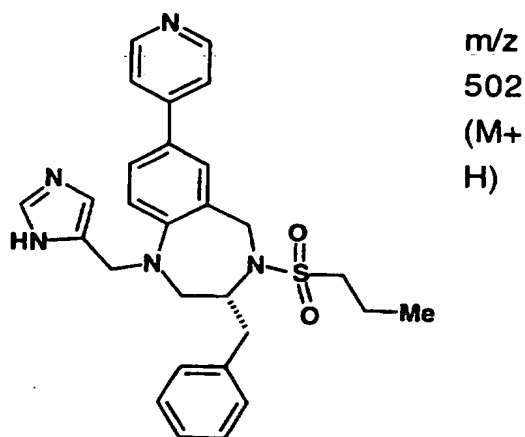
m/z
542
(M+
H)

337 (R)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(phenylsulfonyl)-7-(4-pyridinyl)-1H-1,4-benzodiazepine, dihydrochloride. BMS-218963



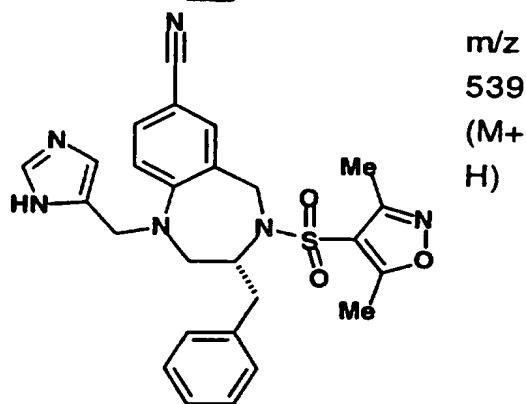
m/z
536
(M+
H)

- 338 (R)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(propylsulfonyl)-7-(4-pyridinyl)-1H-1,4-benzodiazepine, dihydrochloride. BMS-219395



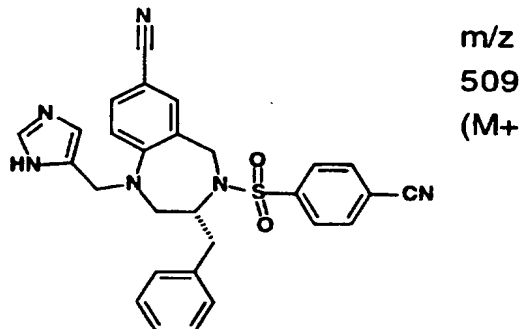
m/z
502
(M+
H)

- 339 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-[(3,5-dimethyl-isoxazol-4-yl)sulfonyl]-1H-1,4-benzodiazepine, dihydrochloride. BMS220904



m/z
539
(M+
H)

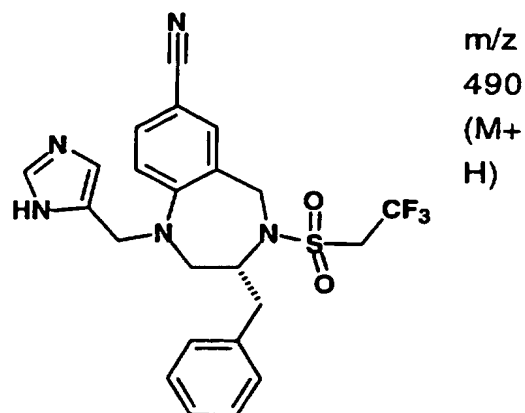
- 340 (R)-7-Cyano-4-[(4-cyanophenyl)sulfonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride. BMS-221604



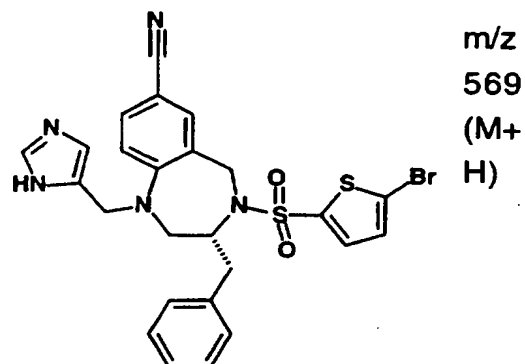
m/z
509
(M+
H)

H)

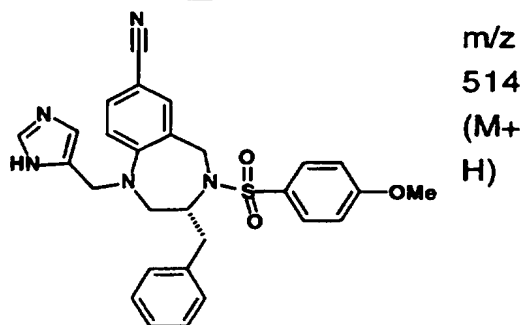
- 341 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-[(2,2,2-trifluoroethyl)sulfonyl]-1H-1,4-benzodiazepine, dihydrochloride. BMS-221764

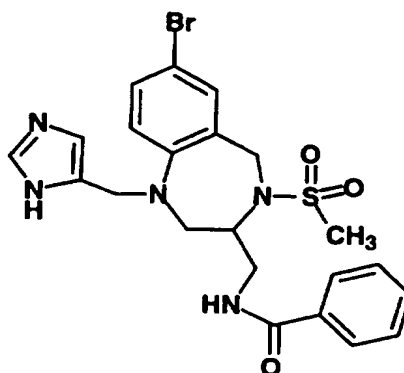


- 342 (R)-[(5-Bromo-2-thienyl)sulfonyl]-7-cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride. BMS-221766



- 343 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[(4-methoxyphenyl)sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride. BMS-221970



Exempl 344

- 5 **N-[[7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-1H-1,4-benzodiazepin-3-yl]methyl]benzamide, dihydrochloride.**

10 **A. N-[[7-Bromo-2,3,4,5-tetrahydro-4-(methylsulfonyl)-1H-1,4-benzodiazepin-3-yl]methyl]benzamide**

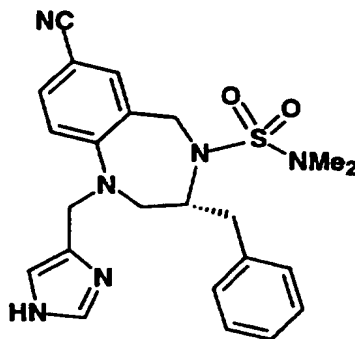
To a solution of Compound C of Example 305 (50 mg, 0.15 mmol) in methylene chloride (10 mL) was added 2,6-di-*tert*-butyl-4-methylpyridine (62 mg, 0.30 mmol). The solution was cooled to -40°C under N₂. Triflic anhydride (0.85 mL, 0.30 mmol) was added and the solution was stirred under N₂ for 1 h at -40°C. NH₃ gas was added via cannula and bubbling continued for 10 min at -40°C. The solution was slowly warmed to rt with continuous bubbling. Ethyl ether (30 mL) and saturated aqueous sodium bicarbonate solution (30 mL) were added and the layers were separated. The organic layer was washed with 1N aqueous HCl. The aqueous layer was made basic with 5N aq. NaOH and the product was extracted with methylene chloride (30 mL). The organic layer was dried (Na₂SO₄) and concentrated to 5 mL. Benzoic acid (26 mg, 0.21 mmol) and EDC (40 mg, 0.21 mmol) were added and the solution stirred for 16 h and concentrated. The residue was chromatographed (flash silica gel, 1:5-1:1; ethyl acetate:hexane) to give 15 mg (16% for the two steps) of Compound A as a white solid. MS (M+H)⁺ 439.

B. N-[[7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-1H-1,4-benzodiazepin-3-yl]methyl]benzamide, dihydrochloride

Compound B was prepared as a white solid in 16% yield as described for Compound D of Example 224.

MS (M+H)⁺ 518.

Example 345



(R)-7-Cyano-1,2,3,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-N,N-dimethyl-3-(phenylmethyl)-4H-1,4-benzodiazepine-4-sulfonamide, hydrochloride.

A. (R)-7-Cyano-1,2,3,5-tetrahydro-N,N-dimethyl-3-(phenylmethyl)-4H-1,4-benzodiazepine-4-sulfonamide

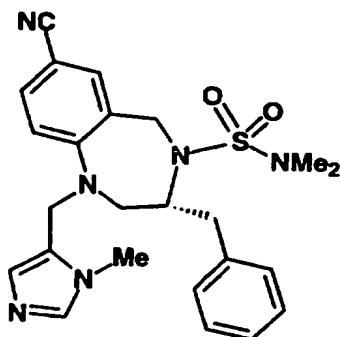
Dimethylsulfamoyl chloride (0.12 mL, 0.16 g, 1.13 mmol) was added to a solution of Compound C of Example 248 (0.2 g, 0.75 mmol) and DIEA (0.19 mL, 1.13 mmol) in acetonitrile (3 mL) at 0°C under argon. After stirring for 16 hr at rt, the reaction was diluted with chloroform (20 mL) and NaHCO₃ (5 mL). The layers were separated and the aqueous layer was extracted with chloroform (2 x 20 mL). The combined organic extracts were washed with NaHCO₃ (2 x 5 mL), water (1 x 10 mL), and brine (2 x 10 mL), dried over MgSO₄, filtered and concentrated. The residue was purified on a flash silica column eluting with 30% EtOAc in hexane to afford Compound A as a yellow oil (0.14 g, 51%). MS [M+H]⁺ = 371⁺.

B. (R)-7-Cyano-1,2,3,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-N,N-dimethyl-3-(phenylmethyl)-4H-1,4-benzodiazepine-4-sulfonamide, hydrochloride

A solution of Compound A (0.068 g, 0.18 mmol), 4-formylimidazole (0.017 g, 0.18 mmol) and AcOH (0.5 mL) in dichloroethane (0.5 mL) and 3A mol. sieves was refluxed for 1 hr. Sodium triacetoxyborohydride (0.038 g, 0.18 mmol) was added. Every day for 6 days additional aldehyde and sodium triacetoxyborohydride were added (1 eq each). After stirring for 6 days, the mixture was diluted with CHCl_3 (10 mL), NH_4OH (5 mL) and NaHCO_3 (5 mL), and stirred for 30 min. The layers were separated and the aqueous layer was extracted with CHCl_3 (3 x 30 mL). The combined organic extracts were dried over MgSO_4 , filtered and concentrated. The product was purified by preparative HPLC (gradient of aqueous methanol with 0.1 % TFA) to afford Compound B as a light yellow solid (40 mg, 50%).

MS $(\text{M}+\text{H})^+ = 451$

Example 346

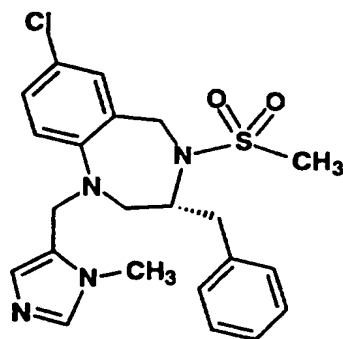


(R)-7-Cyano-1,2,3,5-tetrahydro-N,N-dimethyl-1-[(1-methyl-1H-imidazol-5-yl)methyl]-3-(phenylmethyl)-4H-1,4-benzodiazepine-4-sulfonamide, hydrochloride.

A solution of Compound A of Example 345 (0.068 g, 0.18 mmol), 1-methyl-5-formylimidazole (0.041 g, 0.36 mmol), AcOH (0.2 mL) and 3A mol. sieves in dichloroethane (0.5 mL) was warmed for 2 hr. Sodium triacetoxyborohydride (0.076 g, 0.36 mmol) was added. Additional aldehyde and sodium triacetoxyborohydride (2 eq each) were added at 1.5, 3 and 4.5 hours. After stirring for 2 days, the mixture was diluted with CHCl_3 (10 mL), NH_4OH (5 mL) and NaHCO_3 (5 mL), and stirred for 30 min. The layers were

separated and the aqueous layer was extracted with CHCl_3 (3 x 30 mL). The combined organic extracts were washed with NaHCO_3 and brine (each 2 x 5 mL), dried over MgSO_4 , filtered and concentrated. The product was purified by reverse phase preparative HPLC (gradient of aq methanol with 0.1% TFA) and converted to its HCl salt to afford Example 246 as a light yellow solid (32 mg, 38%).
MS $(\text{M}+\text{H})^+$ 465

10

Example 347

15 **(R)-7-Chloro-2,3,4,5-tetrahydro-1-[(1-methyl-1H-imidazol-5-yl)methyl]-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.**

A. (R)-7-Chloro-2,3,4,5-tetrahydro-3-(phenylmethyl)-1H-1,4-benzodiazepin-2,5-dione

20 A mixture of chloroisatoic anhydride (25 g, 0.126 mol), D-Phe methyl ester (27.2 g, 0.126 mol) and DMAP (0.4 g) in pyridine (275 mL) was refluxed for 5 days. The mixture was concentrated and dissolved in CH_2Cl_2 . The solution was washed with 10% HCl (3 x 100 mL), dried over MgSO_4 , filtered and concentrated to afford a pink solid (39 g) which was
25 recrystallized 3 times from ether/ CH_2Cl_2 to afford Compound A (15.0 g, 40 %). MS $[\text{M}+\text{H}]^+ = 301^+$.

B. (R)-7-Chloro-2,3,4,5-tetrahydro-3-(phenylmethyl)-1H-1,4-benzodiazepine

Borane in THF (1M, 300 mL) was added to Compound A (20 g, 66.5 mmol) in THF (200 mL). The mixture was refluxed for 1 day, cooled in an ice bath, MeOH (115 mL) added slowly, and the mixture concentrated. The residue was diluted with MeOH (200 mL), 40 mL of 25% HCl was added and the mixture was refluxed for 2 hrs and concentrated to dryness to afford an off white solid which was triturated with ether several times and suspended in water. NaOH (1N, to pH 11) was added to the suspension and the solid which formed was filtered, washed with ether, and dried in vacuo to afford 7.9 g of Compound B as a light yellow solid. The filtrate was concentrated to afford an additional 10.5 g of Compound B as a light yellow solid (100 %). MS $[M+H]^+ = 273$

C. (R)-7-Chloro-2,3,4,5-tetrahydro-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine

Methanesulfonyl chloride (3.68 mL, 47.6 mmol) was added dropwise as a solution in CH_2Cl_2 (20 mL) to a solution of Compound B (10 g, 36.6 mmol) in CH_2Cl_2 (130 mL) at 0°C under argon. After stirring at rt for 16 hr the reaction was diluted with water (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 40 mL). The combined organic layers were washed with water (1 x 30 mL), $KHSO_4$ (2 x 30 mL), water (1 x 30 mL), $NaHCO_3$ (2 x 30 mL), brine (1 x 30 mL), dried over $MgSO_4$, filtered and concentrated to afford a golden brown oil. The oil was crystalized from EtOAc/hexanes and the yellow solid triturated with hexane and dried to afford Compound C (10.6 g, 82 %). MS: $[M+H]^+ = 351$

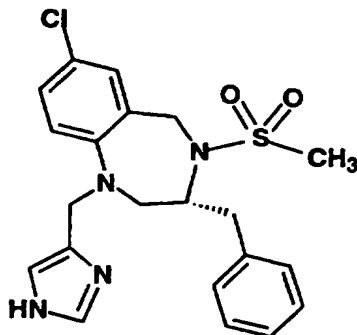
D. (R)-7-Chloro-2,3,4,5-tetrahydro-1-[(1-methyl-1H-imidazol-5-yl)methyl]-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride

Sodium triacetoxyborohydride (4.83 g, 22.8 mmol) was added to a solution of Compound C (4.0 g, 11.4 mmol), 1-methyl-5-formylimidazole (2.6 g, 22.8 mmol) and AcOH (22 mL) in CH_2Cl_2 (22 mL). After stirring for 2 days, the mixture was diluted with CH_2Cl_2 (30 mL), NH_4OH (30 mL) and $NaHCO_3$ (30 mL), and stirred for 30 min. The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with $NaHCO_3$, water, brine (3 x 30 mL), dried over $MgSO_4$,

filtered and concentrated to afford 6.0 g of a foamy solid. The product was purified on a flash column eluting with 7/3 EtOAc/hexane (1L) and 19/1 CHCl₃/MeOH (2L) to afford a white foamy solid, which was treated with 1 N HCl in ether (2 x 25 ml). The solid was triturated with ether and dried to afford Compound D as a light yellow solid (3.44 g, 63 %).

MS (M+H)⁺ 445

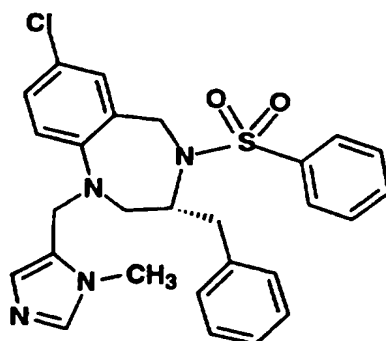
Example 348



(R)-7-Chloro-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.

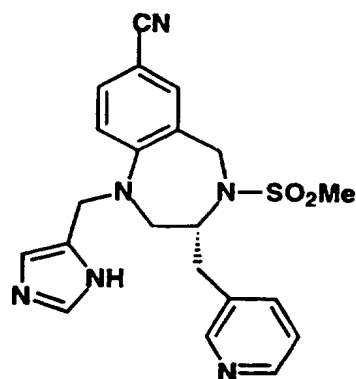
Example 348 was prepared as a light yellow solid in 70% yield from Compound C of Example 247 as described for Compound D of Example 247, using 4-formylimidazole and with refluxing for 1 hour and stirring at rt for 16 hours.

MS (M+ H)⁺ = 431

Exempl 349

- 5 **(R)-7-Chloro-2,3,4,5-tetrahydro-1-[(1-methyl-1H-imidazol-5-yl)methyl]-4-(phenylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.**

10 Example 249 was prepared as a light yellow solid from Compound B of Example 247 by the following sequence: Compound C of Example 247, with benzenesulfonyl chloride, with stirring at rt for 3 hours and chromatography on silica with 7/3 hexanes/EtOAc (57 %); Compound D of Example 247, with stirring at rt for 12 hours and with stirring for 2 days following addition of another equivalent of hydride and aldehyde, and with
15 purification by reverse phase HPLC (gradient of aqueous methanol with 0.1% TFA; 52%).
MS (M+ H)⁺ = 507.

Example 350

5 **(R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(pyridin-3-ylmethyl)-4-(methylsulfonyl)-1H-1,4-benzodiazepine, tetrahydrochloride.**

A. (R)-7-Bromo-2,3,4,5-tetrahydro-3-(pyridin-3-ylmethyl)-1H-1,4-benzodiazepine

10 Borane-THF (1M, 168 ml, 0.168 mmol) was added dropwise to a solution of (R)-7-bromo-2,3,4,5-tetrahydro-3-(pyridin-3-ylmethyl)-1H-1,4-benzodiazepin-2,5-dione (prepared from 5-bromoisotoic anhydride and D-3-pyridylalanine methyl ester hydrochloride as described for Compound C of Example 226; 11.2 gm, 32.4 mmol) in THF (50 ml) at 0°C. When
15 effervescence ceased, the mixture was heated to reflux for 4h, cooled to 0°C and an additional equivalent of 1M borane-THF (32.4 ml, 32.4 mmol) was added. The mixture was refluxed for 2h, cooled to 0°C and quenched by dropwise addition of 6N HCl (125 ml) followed by refluxing the mixture for 1h. The reaction was cooled to rt and concentrated under vacuum. The
20 solid was dissolved in water (100 ml) and the solution was extracted with Et₂O (3X100 ml). The aqueous layer was cooled to 0°C and sodium hydroxide (50%) was added until the solution became basic. The basic solution was extracted with 9/1 CH₂Cl₂/iPrOH (3X200 ml). The combined organic extracts were dried (MgSO₄), filtered and concentrated under
25 vacuum to afford Compound A (8.0 gm, 80%). MS (M+H)⁺ 318, 320.

B. (R)-7-Cyano-2,3,4,5-tetrahydro-3-(pyridin-3-ylmethyl)-1H-1,4-benzodiazepine

30 Copper cyanide (2.6 gm, 29 mmol) was added to a nitrogen purged solution of Compound A (8.3 gm, 26 mmol) in NMP (41.5 ml) at room

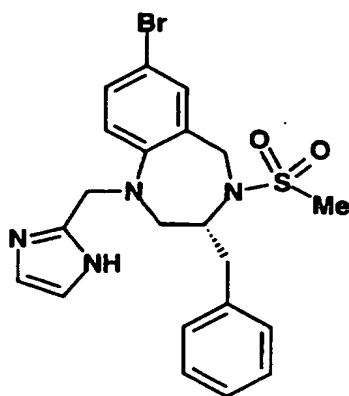
temperature. The mixture was heated to 195°C for 3h, cooled to room temperature and quenched with conc NH_4OH (100 ml). Water was added and the mixture was extracted with 9/1 CH_2Cl_2 /iPrOH (3X200 ml). The combined organic extracts were concentrated under vacuum. The residue was dissolved in 6N HCl (200 ml) and extracted with ethyl acetate (4X200 ml). The aqueous solution was cooled to 0°C, made basic with concentrated ammonium hydroxide and extracted with 9/1 CH_2Cl_2 /iPrOH (3X200 ml). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under vacuum. The residue was flash chromatographed (step gradient, ethyl acetate, 19/1 CH_2Cl_2 /iPrOH, 4/1/0.2 CH_2Cl_2 / MeOH / triethylamine). The appropriate fractions were concentrated under vacuum to afford Compound B (4.1 g, 60%) as a brown solid. MS (M+H)⁺ 265

C. (R)-7-Cyano-2,3,4,5-tetrahydro-3-(pyridin-3-ylmethyl)-4-(methylsulfonyl)-1H-1,4-benzodiazepine

Methylsulfonylchloride (0.031 ml, 0.39 mmol) was added dropwise to a solution of Compound B (0.070 g, 0.27 mmol) and DIEA (0.14 ml, 0.80 mmol) in methylene chloride (2 ml) at -78°C. The mixture was allowed to warm slowly to room temperature and was stirred at rt for 16h. The mixture was quenched with 10% NaHCO_3 (10 ml) and the solution was extracted with methylene chloride (3X10 ml). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under vacuum. The residue was purified by flash chromatography (19/1 methylene chloride/iPrOH) to afford Compound C (0.064 g, 85%) as a solid. MS (M+H)⁺ 343

D. (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(pyridin-3-ylmethyl)-4-(methylsulfonyl)-1H-1,4-benzodiazepine, tetrahydrochloride

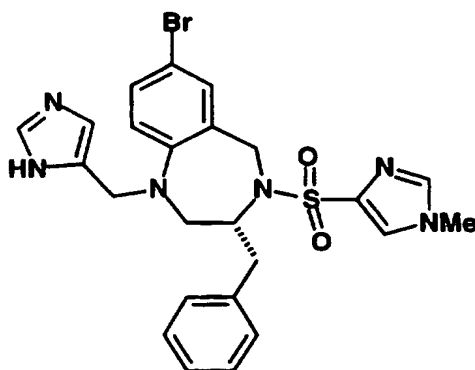
- 4-Formylimidazole (0.062 g, 0.64 mmol) was added to a solution of
- 5 Compound C (0.55 g, 0.16 mmol) and 3A molecular sieves in 1/1 DCE: acetic acid (2 ml) and the mixture was stirred at 70°C for 1h. Sodium triacetoxyborohydride (0.034 g, 0.32 mmol) was added and the mixture was stirred at 70°C for 30 minutes. 4-Formylimidazole (0.032 g, 0.32 mmol) was added and the mixture was stirred at 70°C for 1h. Sodium
- 10 triacetoxyborohydride (0.34 g, 0.32 mmol) was added and the mixture was stirred at 70°C for 30 minutes. The latter two steps were repeated six times. The mixture was cooled to rt, diluted with methylene chloride (30 ml), filtered and the filtrate concentrated under vacuum. The residue was diluted with 25% NH₄OH (50 ml) and the solution was extracted with CH₂Cl₂ (2X200 ml).
- 15 The combined organic extracts were dried (Na₂SO₄), filtered and concentrated under vacuum. The residue was purified by preparative HPLC (gradient of aq MeOH with 0.1% TFA) and the appropriate fractions were concentrated under vacuum. The residue was evaporated from CH₃OH (1 ml) and 1N HCl (1 ml) 4X. The residue was dissolved in CH₃CN (1 ml) and
- 20 1N HCl (1 ml) and lyophilized to afford Compound D (0.040 g, 50 %) as a solid. mp: decomp above 180°C
- MS: (M+H)⁺ 423
- [α]_D = + 89° (c = 0.39, CH₃OH)
- Analysis calculated for C₂₁H₂₂N₆O₂S • 1.4 H₂O • 4 HCl.
- 25 Calc'd: C, 42.44; H, 4.90; N, 14.14.
- Found: C, 42.44; H, 4.66; N, 14.01.

Example 351

- 5 **(R)-7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-2-ylmethyl)-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.**

The product was prepared as an offwhite solid in 54% yield from
 10 Compound C of Example 224 and 2-formyl imidazole as described for Compound D of Example 1.

MS (M+ H)⁺ = 476.

Example 352

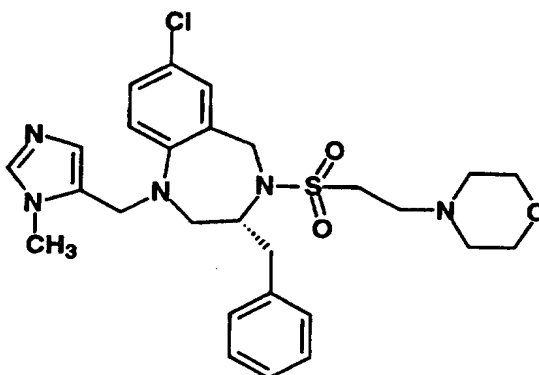
- 15 **(R)-7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[(1-methyl-1H-imidazol-4-yl)sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, trihydrochloride.**
- 20

Example 352 was prepared as an offwhite solid in 54% yield from Compound B of Example 224 and 1-methylimidazole-4-sulfonyl chloride as described for Compounds C and D of Example 224.

MS (M+ H)⁺ = 542.

5

Example 353



10 **(R)-7-Chloro-2,3,4,5-tetrahydro-1-(1-methyl-imidazol-5-ylmethyl)-4-[(2-morpholin-4-yl-ethyl)sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.**

15 **A. (R)-7-Chloro-2,3,4,5-tetrahydro-4-(ethenylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine**

To a solution of 4.4g (16.1 mmol) of Compound B of Example 347 in 75 ml of methylene chloride, at -78 °C and under argon, was added dropwise approximately one-half of a solution of 2.5 ml (24.2 mmol) of 2-chlorosulfonyl chloride in 15 ml of methylene chloride. Then was added rapidly dropwise 5 ml of DIPEA, followed by the remaining sulfonyl chloride solution and an additional 2.4 ml of DIPEA (total 7.4 ml, 40.3 mmol). The resulting pale yellow solution was stirred at -78°C for 0.5 hr, allowed to warm to rt and reduced to one-half volume. The solution of crude Compound A was used directly.

25

B. (R)-7-Chloro-2,3,4,5-tetrahydro-4-[(2-morpholin-4-yl-ethyl)sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine

Morpholine (15 ml) was added rapidly dropwise to the solution of Compound A and stirring was continued overnight at rt. The reaction was washed with water and brine, dried (MgSO₄) and the solvent removed to

30

give an orange oil residue, which was subjected to flash chromatography on a silica gel (5% ethyl acetate-hexane) to afford 3.9 g (54%) of Compound B as a solid white foam.

5 **C. (R)-7-Chloro-2,3,4,5-tetrahydro-1-(1-methyl-imidazol-5-ylmethyl)-4-[(2-morpholin-4-yl-ethyl)sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.**

To a solution of 3.9 g (8.7 mmol) of Compound B in 40 ml of methylene chloride and 4 ml of acetic acid, at rt and under argon, was added
10 3.8 g (34 mmol) of 1-methyl-5-imidazolecarboxaldehyde. After stirring 0.5 hr, 1.9 g (9 mmol) of sodium triacetoxyborohydride was added and the solution heated at 40°C. Additional 1.9 g portions of hydride were added at 1 and 2.5 hours. At 4 hr an additional 1.0 g of aldehyde and 1.9 g of hydride were added and stirring was continued overnight at rt. The reaction was
15 evaporated to dryness and the residue diluted with ethyl acetate and sat NaHCO₃. Additional solid NaHCO₃ was added in portions until the aqueous layer remained alkaline. The organic layer was separated and the aqueous layer extracted twice more with ethyl acetate. The combined organic fractions were washed with brine, dried (MgSO₄) and the solvent removed to
20 give a viscous oil residue, which was purified by flash chromatography on silica (10% methanol-chloroform) followed by preparative HPLC (gradient of aqueous methanol with 0.1%TFA) to afford 3.2 g of the free base as a solid white foam. To a solution of the free amine in ethyl acetate was added excess 1M HCl-ether and the resulting white precipitate collected by filtration
25 to afford 3.2 g (63%) of Compound C as a white powder.

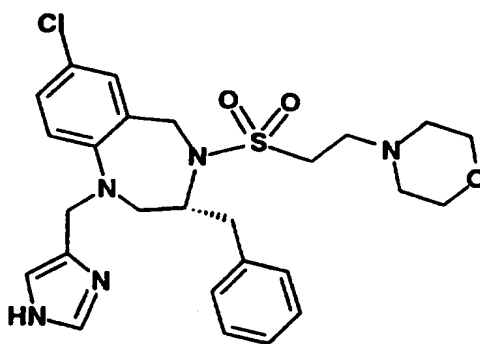
MS: (M+H)⁺ 544

Analysis calculated for C₂₇H₃₄N₅O₃SCl•2HCl•H₂O.

Calc'd: C, 51.07; H, 6.03; N, 11.03.

Found: C, 50.76; H, 5.94; N, 11.13.

30

Example 354

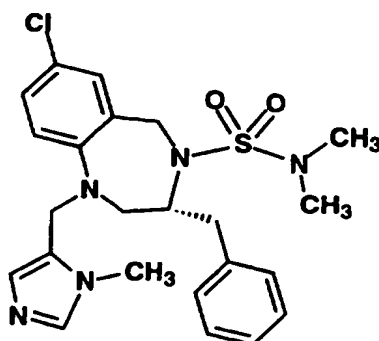
- 5 **(R)-7-Chloro-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[(2-morpholin-4-yl-ethyl)sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.**

10 A mixture of Compound B of Example 353 (0.10 g, 0.22 mmol), 4-formylimidazole (0.042 g, 0.32 mmol), 3A sieves and AcOH (0.3 mL) was refluxed in dichloroethane (0.3 mL) under argon for 2 hours. Sodium triacetoxyborohydride (0.07 g, 0.32 mmol) was added and the mixture was refluxed for 1 hour, stirred at rt for 16 hr, and diluted with CHCl₃, NH₄OH, and NaHCO₃ (each 5 mL). The layers were separated and the aqueous layer

15 was extracted with CHCl₃ (2 x 20 mL). The combined organic extracts were washed with water and brine (each 2 x 5 mL), dried over MgSO₄, filtered and concentrated. The residue was purified by preparative HPLC (gradient of aqueous MeOH with 0.1% TFA). The appropriate fractions were concentrated and the residue evaporated from MeOH (1 mL) and 1N HCl (1

20 mL) 3 times. The residue was dissolved in water and lyophilized to afford Example 354 (0.034 g, 29%) as a solid.

MS (M-H)⁻ = 529.

Example 355

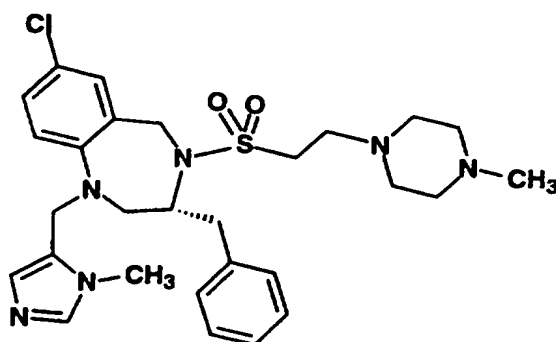
- 5 **(R)-7-Chloro-4-[(dimethylamino)sulfonyl]-1-[(1-methyl-1H-imidazol-5-yl)methyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.**

10 **A. (R)-7-Chloro-4-[(dimethylamino)sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine**

Dimethylsulfamoyl chloride (0.058 mL, 0.54 mmol) was added dropwise to a solution of Compound B of Example 347 (0.1 g, 0.36 mmol) and DIEA (0.095 mL, 0.54 mmol) in CH₃CN (2 mL) at 0°C under argon. The mixture was slowly warmed to rt over 16 hr and diluted with NaHCO₃ (3 mL) and CHCl₃ (10 mL). The layers were separated and the aqueous layer was extracted with CHCl₃ (2 x 30 mL). The combined organic layer was washed with NaHCO₃ (1 x 10 mL), water (1 x 10 mL) and brine (1 x 10 mL), dried over MgSO₄, filtered and concentrated to afford an orange oil, which was purified on a silica gel flash column (30 % EtOAc/hexane) to afford Compound A as a clear oil 2 (0.44 g, 32 %). MS (M+H)⁺ 380.

25 **B. (R)-7-Chloro-4-[(dimethylamino)sulfonyl]-1-[(1-methyl-1H-imidazol-5-yl)methyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride**

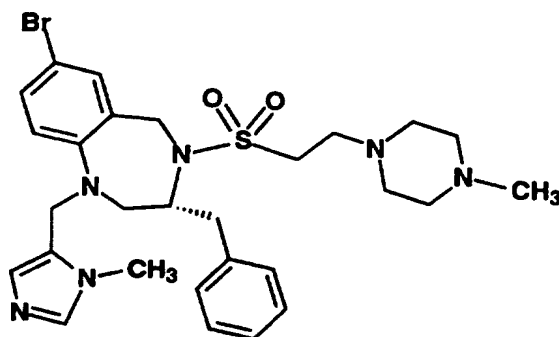
Compound B was prepared as a white solid in 52% yield from Compound A as described for Compound C of Example 353, with refluxing for 4 hours and with purification only by preparative HPLC. MS (M+H)⁺ 474.

Exempl 356

5 **(R)-7-Chloro-2,3,4,5-tetrahydro-1-(1-methyl-imidazol-5-ylmethyl)-4-[(4-methyl-piperidin-4-yl-ethyl)sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.**

Example 356 was prepared as a light yellow solid in 28% yield from Compound A of Example 353 and 1-methylpiperazine as described for
10 Compound B of Example 353, with chromatography using 20% acetone in hexane followed by 10% methanol in CHCl_3 and Compound C of Example 353, with purification by preparative HPLC only.
MS: $[\text{M}+\text{H}]^+ = 557$.

15

Example 357

20 **(R)-7-Bromo-2,3,4,5-tetrahydro-1-(1-methyl-imidazol-5-ylmethyl)-4-[(4-methyl-piperidin-4-yl-ethyl)sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.**

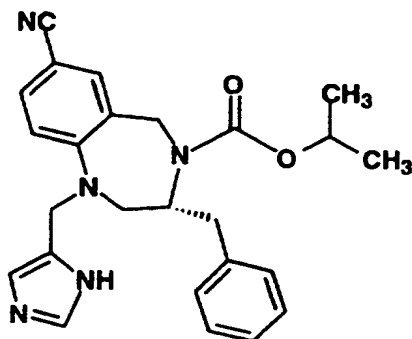
Example 357 was prepared as a white solid in 23% yield from Compound B of Example 224 and 1-methylpiperazine as described by the following sequence: Compound A of Example 353; Compound B of Example

353, with chromatography using 9/1 CHCl_3 / MeOH; Compound C of Example 353, with purification by preparative HPLC only.

MS: $[\text{M}+\text{H}]^+ = 601$.

5

Example 358



(R)-7-Cyano-1,2,3,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4H-1,4-benzodiazepine-4-carboxylic acid, isopropyl ester, hydrochloride.

10

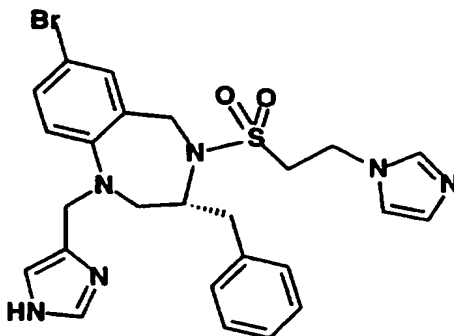
Example 358 was prepared as a light yellow solid in 42% yield from Compound C of Example 248 by the following sequence: Compound E of Example 248, using a toluene solution of isopropyl chloroformate with chromatography using 40% hexane in EtOAc and with the free base carried on; Example 354.

15

MS: $[\text{M}+\text{H}]^+ = 430$.

Example 359

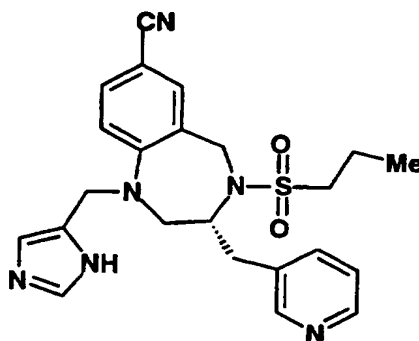
20



(R)-7-Bromo-2,3,4,5-tetrahydro-4-[[2-(1H-imidazol-1-yl)thyl] sulfonyl]-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.

Example 359 was prepared as a light yellow solid in 21% yield from Compound B of Example 224 as described in the following sequence: Compound A of Example 353; Compound B of Example 353, using sodium imidazolate, 2:1 THF:IPA as solvent, and chromatography using 10% EtOAc in CHCl₃ followed by EtOAc; Compound C of Example 353, with addition of aldehyde and hydride every day for 8 days, and no purification.
MS: [M+H]⁺ = 557.

10

Example 360

(R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(propylsulfonyl)-3-(3-pyridinylmethyl)-1H-1,4-benzodiazepine, hydrochloride.

15

Example 360 was prepared as a white solid in 15% yield from n-propanesulfonylchloride and Compound B of Example 350 as described for Compounds C and D of Example 350.

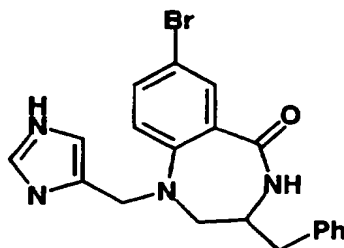
MS: (M+H)⁺ 451

20

Analysis calculated for C₂₃H₂₆N₆O₂S • 2.6 HCl • 2.02 H₂O.

Calc'd: C, 47.50; H, 5.65; N, 14.45.

Found: C, 47.50; H, 5.51; N, 14.10.

Example 361

5 **7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepin-5-one, hydrochloride.**

A. 7-Bromo-2,3,4,5-tetrahydro-3-(phenylmethyl)-1H-1,4-benzodiazepin-5-one

10 To a suspension of 0.5 g (1.45 mmol) of Compound A of Example 75 in 5 ml of THF, at rt and under argon, was added 3 ml (3 mmol) of 1 M borane in THF. Stirring was continued overnight, after which an additional 2 ml (2 mmol) of 1 M borane in THF was added and stirring continued an additional 8 hr. After hydrolysis of excess borane by the dropwise addition of methanol, the reaction was evaporated to dryness and the residue dissolved in 0.5 ml each of methanol and conc HCl. The resulting solution was heated at reflux for 2 hr, cooled to rt and evaporated to dryness. The residue was evaporated from methanol an additional three times. The crude product was dissolved in ethyl acetate and the solution washed with brine, dried, and the solvent removed to afford a viscous yellow oil, which was subjected to flash chromatography on silica gel (50% ethyl acetate/hexane) to give 205 mg (43%) of Compound A as a white solid.

B. 7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepin-5-one, hydrochloride

25 To a suspension of 205 mg (0.62 mmole) of Compound A in 10 ml of methylene chloride and 1 ml of acetic acid was added 120 mg (1.25 mmol) of 4-formylimidazole. The solution was stirred 1 hr, 197 mg (0.93 mmol) of sodium triacetoxyborohydride was added and stirring continued overnight. An additional 60 mg of 4-formylimidazole and 100 mg of sodium triacetoxyborohydride were added and stirring continued an additional 4 hr. The reaction was evaporated to dryness. The residue was diluted with methylene chloride and the solution washed with sat. NaHCO₃ and brine, dried (MgSO₄), and the solvent removed to afford a pale yellow solid foam

residue, which was subjected to preparative HPLC (gradient of aqueous methanol with 0.1% TFA). Concentration of the appropriate fractions afforded a clear oil residue which was converted to the HCl salt by treatment with HCl-MeOH to give 187 mg (60%) of Compound B as a near white solid.

5 MS: (M+H)⁺ 411.

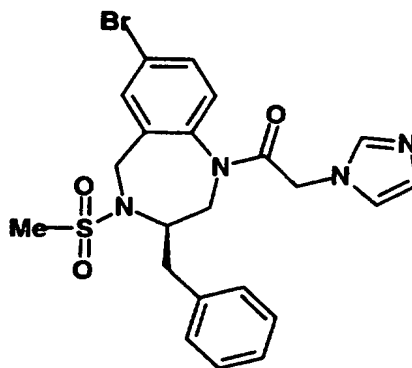
Analysis calculated for C₂₀H₁₉N₄OBr • 1.5 HCl • 0.5 C₂H₁₀O.

Calc'd: C; 52.53, H; 5.11, N; 11.14.

Found: C; 52.82, H; 4.71, N; 11.52.

10

Example 362



15 **(R)-7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-1-ylacetyl)-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate.**

A. (R)-7-Bromo-2,3,4,5-tetrahydro-1-(chloroacetyl)-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine

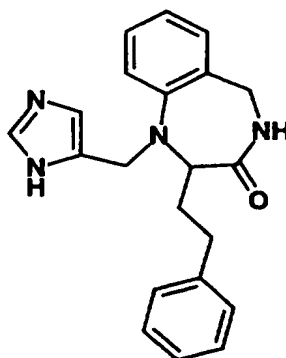
20 To a mixture of Compound C of Example 224 (2.0 g, 5.06 mmol) and DIEA (4.4 mL, 25 mmol) in dichloromethane (100 mL) in an ice bath under argon, was added chloroacetyl chloride (2.0 mL, 25.3 mmol). The mixture was stirred for 30 min, poured into aqueous sodium hydroxide (200 mL, 1 N) and extracted with dichloromethane (2 x 100 mL). The organic
25 layers were combined, washed with brine (200 mL), and water (200 mL), dried (MgSO₄) and concentrated to an oil, which was purified by flash chromatography (60 g silica, 3:1 hexane : ethylacetate) to provide Compound A (760 mg, 1.62 mmol, 33 %) as a colorless oil.

B. (R)-7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-1-ylacetyl)-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate

A mixture of Compound A (300 mg, 0.64 mmol), potassium carbonate (177 mg, 1.28 mmol) and imidazole (87 mg, 1.28 mmol) was stirred for 48 hours. The mixture was poured into aqueous hydrochloric acid (200 mL, 1 N) and ethyl acetate (200 mL), separated, and the aqueous adjusted to pH 11 with solid sodium hydroxide. The basic aqueous solution was extracted with ethyl acetate (200 mL) and the organic extracts were combined and dried (Na₂SO₄), and concentrated in vacuo to a semi-solid which was purified by preparative HPLC (aqueous methanol gradient containing 0.1% trifluoroacetic acid, C-18 column) and lyophilized to provide Compound B as a white solid (100 mg, 32 %).

MS: (M+H)⁺ 504

Example 363



1,2,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-2-(2-phenylethyl)-3H-1,4-benzodiazepin-3-one.

A. 1,2,4,5-Tetrahydro-2-(2-phenylethyl)-3H-1,4-benzodiazepin-3-one

To a stirred solution of N-Boc-(2-amino)-benzylamine (1.0 g, 4.5 mmol) and ethyl 2-oxo-4-phenylbutyrate (1.0 mL, 5.3 mmol) in dichloroethane (20 mL) and acetic acid (1.0 mL) was added NaBH(OAc)₃ in one portion at room temperature under argon. The mixture was allowed to stir for 18 h, TFA (4 mL) was added, and the mixture was heated at 60°C under argon for 2 h. The solvent was removed and the residue was dissolved in methanol (15 mL). The solution was cooled to 0°C, and 10 N

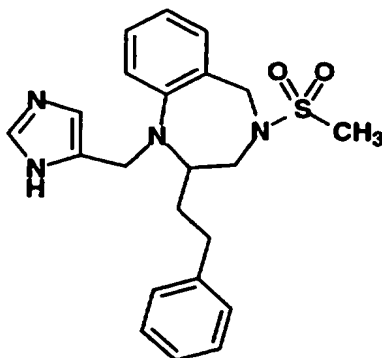
NaOH solution was added to pH 11. The solution was allowed to stir at rt for 18 h. The solvent was removed and the residue was partitioned between ethyl acetate and saturated NaHCO₃ solution. The organic layer was separated, dried over MgSO₄, and concentrated in vacuo. The residue was
5 crystallized from MeOH to give Compound A (480 mg, 40%) as a white solid, mp: 147-148°C.

B. 1,2,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-2-(2-phenylethyl)-3H-1,4-benzodiazepin-3-one

10 Compound B was prepared as a white solid from Compound A as described for Compound D of Example 1.

MS: (M+H)⁺ 347.

Example 364



20 **2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-2-(2-phenylethyl)-1H-1,4-benzodiazepine, monohydrochloride.**

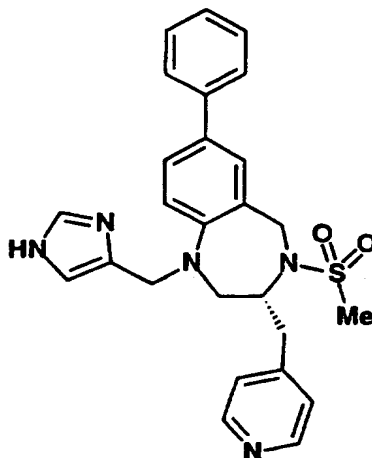
A. 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-2-(2-phenylethyl)-1H-1,4-benzodiazepine

25 To a stirred suspension of lithium aluminium hydride (160 mg) in glyme was added a solution of the free base of Example 363 (150 mg) in glyme at room temperature under argon. The mixture was allowed to stir at room temperature for 18 h, quenched by addition of ethyl acetate (20 mL) followed by ammonium hydroxide (0.5 mL), stirred for 2 h and filtered. The filtrate was concentrated in vacuo to give Compound A as an oil.

30

B. 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-2-(2-phenylethyl)-1H-1,4-benzodiazepine, monohydrochloride

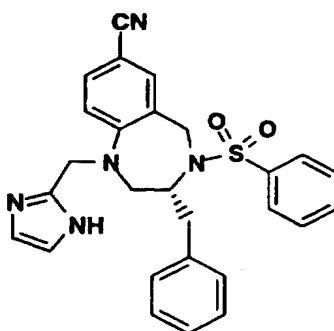
- To a stirred solution of Compound A (50 mg) in methylene chloride (5 mL) in the presence of solid K₂CO₃ was added 100 μ L of methanesulfonyl chloride at room temperature. The solution was stirred for 30 min, diluted with 10 mL of methanol followed by 1 mL of 10N NaOH solution, stirred for 2 h and concentrated. The residue was partitioned between ethyl acetate and saturated NH₄Cl solution. The organic layer was separated, dried over MgSO₄, and concentrated in vacuo. The residue was purified by column chromatography (ethyl acetate/methanol/NH₄OH; 10:1:0.1) to give an oil, which was converted to its HCl salt as described for Compound D of Example 1.
- MS: (M+H) 411.

Example 365

- 5 **(R)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-7-phenyl-3-(4-pyridinylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.**

10 Example 365 was prepared as a light yellow solid in 99% yield from Compound B of Example 226 and D-(4-pyridyl)alanine by the following sequence: Compound C of Example 226; Compound D of Example 226; Compound B of Example 264; Compound D of Example 264.
MS (M+H)⁺ 474.

15

Example 366

- 20 **(R)-2,3,4,5-Tetrahydro-1-(1H-imidazol-2-ylmethyl)-4-(phenylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine-7-carbonitril, hydr chlorid .**

Example 366 was prepared as a yellow solid in 95% yield from Compound A of Example 312 and 2-formyl imidazole as described for Compound D of Example 1.

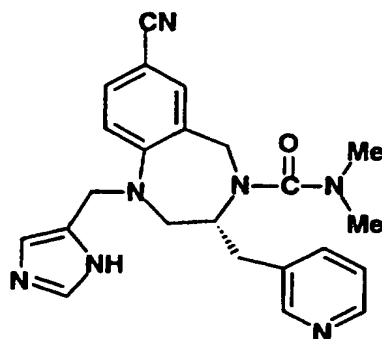
MS (M+H)⁺ = 484.1.

5 Analysis calculated for C₂₇H₂₅N₅O₂S • 0.6 H₂O • 1.1 HCl.

Calc'd: C, 60.67; H, 5.15; N, 13.10; S, 5.99; Cl, 7.29.

Found: C, 60.34; H, 5.16; N, 12.81; S, 5.74; Cl, 7.46.

Example 367



10

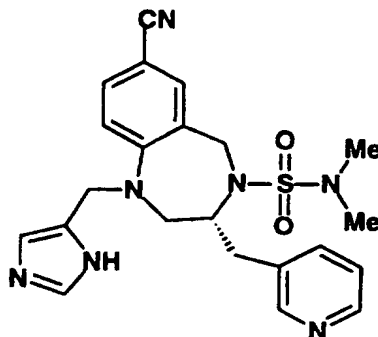
15

(R)-7-Cyano-1,2,3,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-N,N-dimethyl-3-(3-pyridinylmethyl)-4H-1,4-benzodiazepine-4-carboxamide, dihydrochloride.

20

Example 367 was prepared as a solid in 2% yield from N,N-dimethylcarbamoyl chloride and Compound B of Example 350 as described in the following sequence: Compound C of Example 350, with extraction using 10% isopropanol/methylene chloride; Compound D of Example 350, with extraction using 10% isopropanol/methylene chloride and lyophilization from 1N HCl/methanol.

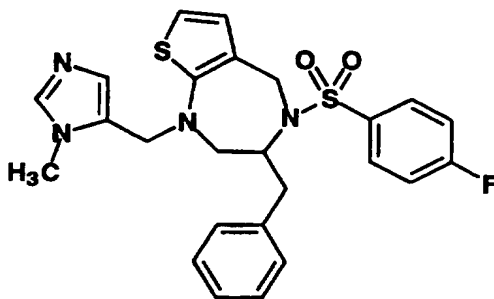
HRMS: (M+H)⁺ Calc : 416.2198; Found: 416.2211.

Example 368

- 5 **(R)-7-Cyano-1,2,3,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-N,N-dimethyl-3-(3-pyridinylmethyl)-4H-1,4-benzodiazepine-4-sulfonamide, dihydrochloride.**

10 Example 368 was prepared as a solid in 1% yield from N,N-dimethylsulfamoyl chloride and Compound B of Example 350 as described in Example 367.

HRMS: (M+H)⁺ Calc : 452.1868; Found: 452.1860.

Example 369

15 **4-[(4-Fluorophenyl)sulfonyl]-2,3,4,5-tetrahydro-1-[(1-methyl-1H-imidazol-5-yl)-3-(phenylmethyl)-1H-thieno[2,3-e]-1,4-diazepine, monohydrochloride.**

20 **A. 2,3,4,5-tetrahydro-3-(phenylmethyl)-1H-thieno[2,3-e]-1,4-diazepin-2,5-dione**

A stirred solution of D,L-N-(2-cyano-1-oxoethyl)-phenylalanine, methyl ester (5.0 g, 20 mmol), dithianediol (1.6 g, 10.5 mmol), pipridine (2.0

mL, 20.2 mmol) and TEA (2.8 mL, 20.2 mmol) in ethanol (30 mL) was heated at reflux for 3 h and evaporated. The residue was evaporated from toluene three times. The dry residue was dissolved in pyridine, and pyridinium chloride (2.0 g) was added. The solution was heated under argon at 130°C for 3 days and evaporated. The residue was dissolved in methylene chloride and the solution was washed with 1 N HCl solution (2 x 100 mL). The organic layer was dried and concentrated in vacuo. The residue was triturated with ether to give Compound A as a brown solid (2.0 g, 40%), mp 268-270 °C.

B. 2,3,4,5-tetrahydro-3-(phenylmethyl)-1H-thieno[2,3-e]-1,4-diazepine

To a stirred suspension of lithium aluminum hydride (400 mg) in glyme was added Compound A (500 mg, 2.05 mmol) in small portions at room temperature under argon. The resultant suspension was heated at reflux for 3 days, cooled to 0°C, and the excess LAH was destroyed by slow addition of ethyl acetate. NH₄OH solution (1 mL) was added and the resultant suspension was filtered and the filter cake was washed with ethyl acetate. The filtrate was concentrated in vacuo. The residue was triturated in ether to give Compound B as a brown solid (220 mg), mp 139-141°C. MS: (M+H)⁺ 245.

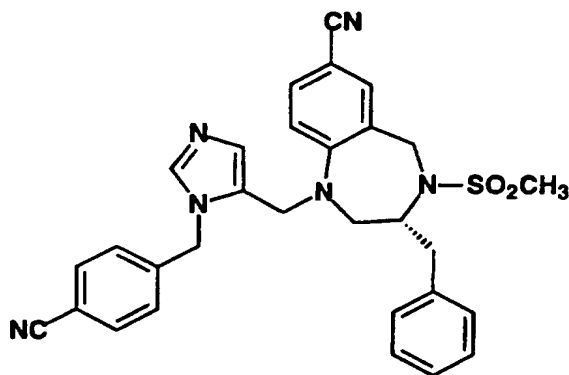
C. 4-[(4-Fluorophenyl)sulfonyl]-2,3,4,5-tetrahydro-3-(phenylmethyl)-1H-thieno[2,3-e]-1,4-diazepine

To a stirred solution of Compound B (150 mg, 0.6 mmol) in methylene chloride with saturated NaHCO₃ solution was added 4-fluorobenzenesulfonyl chloride (300 mg, 1.55 mmol). The mixture was stirred at room temperature for 18 h and diluted with methanol. 10N NaOH was added and the mixture was stirred for 2 h. Concentrated NH₄OH was added and the mixture was stirred for 18 h and concentrated in vacuo. The residue was partitioned between ethyl acetate and saturated NaHCO₃. The organic layer was separated, dried over MgSO₄, and concentrated in vacuo. The residue was purified by chromatography (1:4, ethyl acetate and hexanes) to give Compound C as an oil (120 mg, 50%).

D. 4-[(4-Fluorophenyl)sulfonyl]-2,3,4,5-tetrahydro-1-[(1-methyl-1H-imidazol-5-yl)-3-(phenylmethyl)-1H-benzodiazepin-7-yl]-1,4-benzodiazepine, monohydrochloride

- Compound D was prepared as a solid in 48% yield from
 5 Compound C and 1-methyl-5-formylimidazole as described for Compound D of Example 224.
 MS (M+H)⁺ 497.

Example 370



(R)-2,3,4,5-Tetrahydro-1-(1-(4-cyanophenylmethyl)-imidazol-5-ylmethyl)-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine-7-carbonitrile, hydrochloride.

15

A. (R)-2,3,4,5-Tetrahydro-1-(1-(triphenylmethyl)-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine-7-carbonitrile

- To a solution of 1.2 g (2.85 mmol) of the free base of Example 225
 20 in 20 ml of acetonitrile, at rt and under argon, was added 1.2 ml (8.55 mmol) of TEA, followed by 1.2 g (4.3 mmol) of triphenylmethyl chloride. Stirring was continued overnight. The resulting cloudy solution was evaporated to dryness and the residue subjected to flash chromatography on a 100 cc column of silica gel (50% ethyl acetate-hexane) to afford 1.2 g (64%) of
 25 Cmpd A as a viscous white foam.

B. (R)-2,3,4,5-Tetrahydro-1-(1-(4-cyanophenylmethyl)-imidazol-5-ylmethyl)-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine-7-carbonitrile, hydrochloride

A solution of 200 mg (0.3 mmol) of Compound A and 59 mg (0.3 mmol) of 4-cyanobenzyl bromide in 0.5 ml of DMF was heated at 100°C, under argon, for 10 hr. The reaction was diluted with methylene chloride and 0.1 ml of triethylsilane was added, followed by 0.5 ml of TFA. The mixture was stirred 1 hour and evaporated to give a yellow viscous oil residue which was combined with material obtained from a similar reaction and subjected to silica flash chromatography (2% methanol-chloroform) to afford 76 mg of viscous tan foam. A second silica flash chromatography (1% methanol-chloroform, then 3% methanol-chloroform) afforded 53 mg of the free base of Compound B as a solid white foam. To a solution of 50 mg of free base in ethyl acetate was added 90 µl 1M HCl in ether. The resulting white precipitate was collected by filtration and dried to afford 43 mg (0.07 mmole) of Compound B as a white solid.

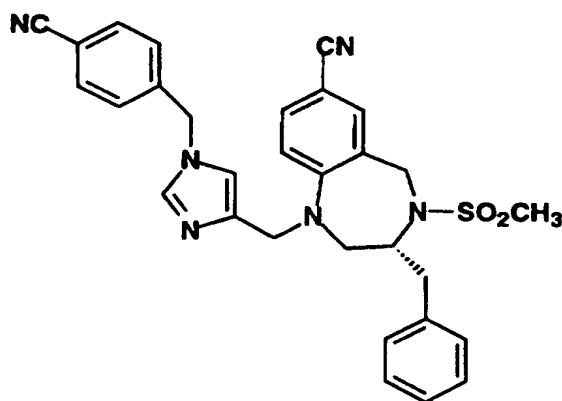
Analysis calculated for $C_{20}H_{28}N_6N_2S \cdot HCl \cdot H_2O$.

Calc'd: C, 60.96; H, 5.29; N, 14.22.

Found: C, 61.11; H, 5.10; N, 14.07.

MS $(M+H)^+ = 537$.

Example 371



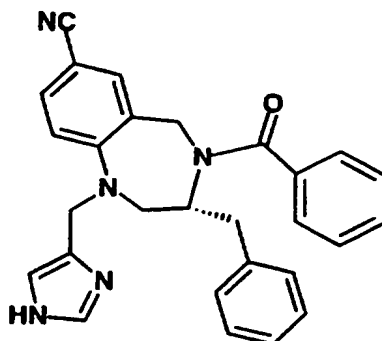
(R)-2,3,4,5-Tetrahydro-1-(1-(4-cyanophenylmethyl)-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine-7-carbonitrile, hydrochloride.

A. (R)-2,3,4,5-Tetrahydro-1-(1-((1,1-dimethyl)-thoxycarbonyl)-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine-7-carbonitrile

To a solution of 250 mg (0.53 mmol) of the free base of Example 225 and 0.6 mg (0.005 mmol) of DMAP in 2 ml of methylene chloride, at rt and under argon, was added a solution of 144 mg (0.66 mmol) of BOC anhydride in 2 ml of methylene chloride. Stirring was continued for 1 hr. The reaction, without workup, was subjected to flash chromatography on a 50 cc column of silica gel (45% ethyl acetate-hexane) to afford 307 mg (approx 100%) of Compound A as a solid white foam.

B. (R)-2,3,4,5-Tetrahydro-1-(1-(4-cyanophenylmethyl)-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine-7-carbonitrile, hydrochloride

A solution of 60 mg (0.115 mmol) of Compound A and 23 mg (0.115 mmol) of 4-cyanobenzyl bromide in 1 ml of DMF was heated at 100°C, under argon, for 10 hr and evaporated. The residue was diluted with methylene chloride and sat NaHCO₃ and stirred for 0.5 hr. The organic layer was separated, dried (MgSO₄) and the solvent removed to yield a clear colorless glass residue. The crude product was subjected to flash chromatography on a 25 cc column of silica gel (1% methanol-chloroform, then 3% methanol chloroform) to afford 6 mg of the free base of Compound B as a solid white foam. To this material in minimal ethyl acetate was added 100 µl 1M HCl in ether. The resulting white precipitate was collected by filtration and dried to afford 4.5 mg (7%) of Compound B as a white solid. MS: (M+H)⁺ 537

Example 372

(R)-4-Benzoyl-7-cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.

A. (R)-4-Benzoyl-7-cyano-2,3,4,5-tetrahydro-3-(phenylmethyl)-1H-1,4-benzodiazepine

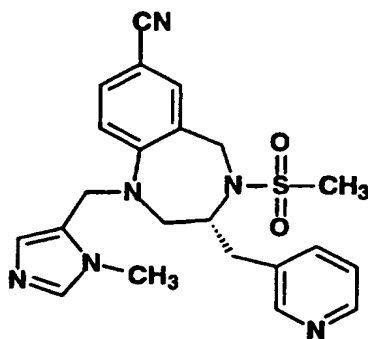
Benzoyl chloride (2.2 mL, 1.9 mmol) was added to a solution of Compound C of Example 248 and DIEA (0.32 mL, 1.99 mmol) in dichloromethane (3 mL) at 0°C under argon. The solution was slowly warmed to rt. At 15 and 30 hr, 0.5 equivalents of benzoyl chloride and DIEA were added. After stirring for 2 days, the mixture was diluted with chloroform (20 mL) and NaHCO₃ (5 mL). The layers were separated, the aqueous layer was extracted with chloroform (2 x 15 mL). The combined organic extracts were washed with NaHCO₃ (2 x 5 mL), water (1 x 10 mL) and brine (2 x 10 mL), dried over MgSO₄, filtered and concentrated. The residue was purified on a flash column eluting with 20% and 30% EtOAc in hexane to afford Compound A as a yellow oil 2 (0.21 g, 77 %). MS (M+H)⁺ 368.

B. (R)-4-Benzoyl-7-cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride

A mixture of Compound A (0.1 g, 0.27 mmol), 4-formylimidazole (0.039 g, 0.40 mmol), AcOH (0.3 mL) in toluene (1 mL) and 3A sieves was refluxed for 15 hrs. Sodium triacetoxyborohydride (0.086 g, 0.4 mmol) was added and the mixture was refluxed for 8 hr, cooled to rt and stirred 15 hours. An additional equivalent of aldehyde was added, the solution was stirred 30 minutes, and an additional equivalent of hydride was added and

the solution was stirred 16 hours. An additional equivalent of aldehyde and hydride was added as above, and the mixture was stirred 4 hours, diluted with CHCl_3 (10 mL), NH_4OH (5 mL) and NaHCO_3 (5 mL), and stirred for 10 min. The layers were separated and the aqueous layer was extracted with CHCl_3 (3 x 30 mL). The combined organic extracts were washed with NaHCO_3 , water, and brine (each 2 x 10 mL) dried over MgSO_4 , filtered and concentrated. The product was purified by preparative HPLC, (gradient of aqueous MeOH with 0.1 % TFA). The appropriate fractions were concentrated under vacuum. The residue was evaporated from MeOH (1 mL) and 1 N HCl (1 mL) three times. The residue was dissolved in water and lyophilized to afford Compound B as a light yellow solid (36 mg, 30 %). MS ($\text{M} + \text{H}$)⁺ = 448.

Example 373



(R)-7-Cyano-2,3,4,5-tetrahydro-1-[(1-methyl-1H-imidazol-5-yl)methyl]-3-(pyridin-3-ylmethyl)-4-(methylsulfonyl)-1H-1,4-benzodiazepine, dihydrochloride.

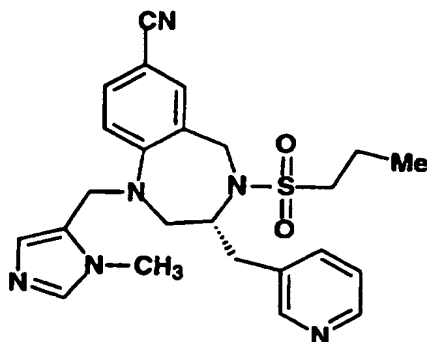
Example 373 was prepared as a solid in 13% yield from Compound B of Example 350 as described for Compound C of Example 350 and Compound D of Example 350, using 1-methyl-5-formylimidazole.

MS: ($\text{M} + \text{H}$)⁺ 437

Analysis calculated for $\text{C}_{22}\text{H}_{24}\text{N}_6\text{O}_2\text{S} \cdot 2 \text{HCl} \cdot 2.1 \text{H}_2\text{O}$.

Calc'd: C, 48.28; H, 5.56; N, 15.36.

Found: C, 48.28; H, 5.42; N, 15.45.

Example 374

5 **(R)-7-Cyano-2,3,4,5-tetrahydro-1-[(1-methyl-1H-imidazol-5-yl)methyl]-3-(pyridin-3-ylmethyl)-4-(propylsulfonyl)-1H-1,4-benzodiazepine, trihydrochloride.**

Example 374 was prepared as a solid in 11% yield from propanesulfonyl chloride as described for Example 373.

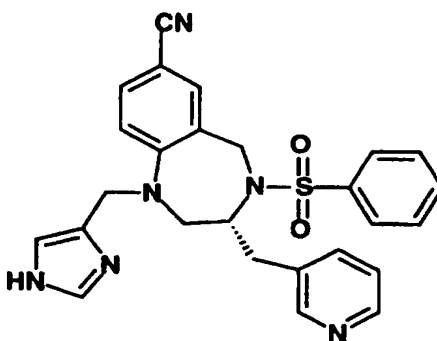
10 MS: (M+H)⁺ 465

Analysis calculated for C₂₄H₂₈N₆O₂S • 3 HCl • 0.26 H₂O.

Calc'd: C, 49.82; H, 5.49; N, 14.52.

Found: C, 49.81; H, 5.37; N, 14.58.

15

Example 375

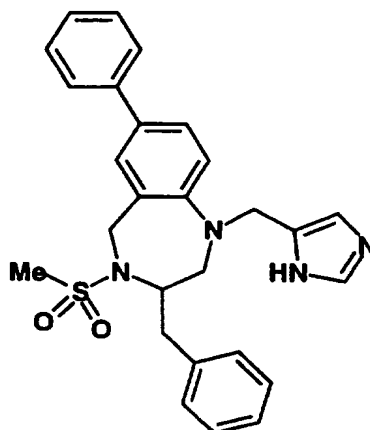
20 **(R)-7-Cyano-2,3,4,5-tetrahydro-1-[(1H-imidazol-4-yl)methyl]-3-(pyridin-3-ylmethyl)-4-(phenylsulfonyl)-1H-1,4-benzodiazepine, dihydrochloride.**

Example 375 was prepared as a solid in 2% yield from Compound B of Example 350 as described for Compound C of Example 350 using benzenesulfonyl chloride, and Compound D of Example 350.

MS: (M+H)⁺ 485

5

Example 376



10 **2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-7-phenyl-3-(phenylmethyl)-1H-1,4-benzodiazepine.**

15 **A. 2,3,4,5-Tetrahydro-7-phenyl-3-(phenylmethyl)-1H-1,4-benzodiazepine**

To a mixture of Compound B of Example 75 (200 mg, 0.63 mmol) in toluene (20 mL) and aq sodium bicarbonate (10 mL, saturated solution) under argon was added a solution of phenylboronic acid (153 mg in 5 mL abs ethanol). Tetrakis(triphenylphosphine) palladium(0) (36 mg) was added, and the solution was heated to reflux (~80°C) for 18 hours, cooled to room temperature and partitioned between aqueous sodium hydroxide (100 mL, 3N) and ethyl acetate (100 mL). The mixture was extracted with ethyl acetate (2 x 200 mL) and the organic layers were combined, dried (MgSO₄) and concentrated in vacuum to a crude oil which was purified using flash chromatography (silica, 10:0.5: 0.05 ethyl acetate : methanol : ammonium hydroxide) to provide Compound A (90 mg, 45 %) as a waxy solid.

B. 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-7-phenyl-3-(phenylmethyl)-1H-1,4-benzodiazepine

Compound B was prepared as a white solid in 40% yield from Compound A as described in the following sequence: Compound A of Example 78, with stirring for 18 hours and no chromatography; Compound B of Example 78.

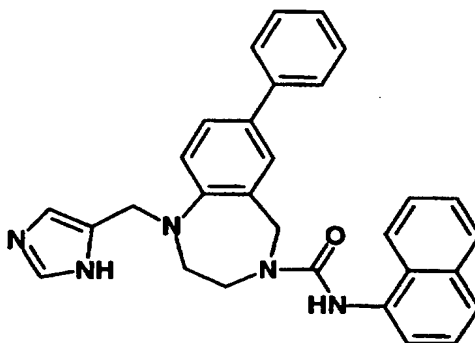
MS: (M+H)⁺ 473

Analysis calculated for C₂₇H₂₈N₄O₂ · 0.5 H₂O · 0.8 TFA.

Calc'd: C, 59.97; H, 5.24; N, 9.78; S, 5.60; F, 7.96.

Found: C, 59.94; H, 4.87; N, 8.21; S, 4.48; F, 7.86.

Example 377



1,2,3,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-N-(1-naphthalenyl)-7-phenyl-4H-1,4-benzodiazepine-4-carboxamide, monohydrochloride.

A. 1,2,3,5-Tetrahydro-N-(1-naphthalenyl)-7-phenyl-4H-1,4-benzodiazepine-4-carboxamide

Compound B of Example 12 (148 mg, 0.66 mmol) was added to 1-naphthylisocyanate (116 mg, 0.66 mmol) in 3 mL of dry CH₂Cl₂ under argon and the mixture was stirred for 16 hours and concentrated to give crude compound A (267 mg).

B. 1,2,3,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-N-(1-naphthalenyl)-7-phenyl-4H-1,4-benzodiazepine-4-carboxamide, monohydrochloride

Compound B was prepared as a light pink solid in 46% yield from Compound A as described for Compound D of Example 1. mp 170-177°C dec.

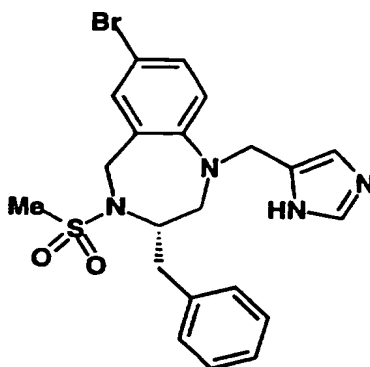
MS: (M+H)⁺ 474

Analysis calculated for C₃₀H₂₇N₅O • 1.2 HCl • 0.6 H₂O • 0.25 Et₂O.

Calc'd: C, 68.11; H, 5.88; N, 12.81; Cl, 7.78.

Found: C, 68.02; H, 5.92; N, 12.61; Cl, 7.75.

Example 378



(S)-7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, hydrochloride.

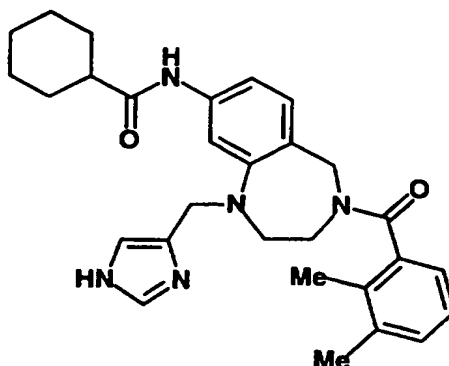
A solution of the free base of Example 78 (100 mg, 0.31 mmol) in isopropanol (5 mL) was purified using chiral-phase preparative HPLC (chiralpak AD column produced by Chiral Technologies Inc. (50 mm x 500 mm), 25:75:0.1 isopropanol:hexane:triethylamine, flow rate 55 ml/min) to provide isomer A at 36 min (18 mg, 13%, free base of Example 378) and isomer B at 54 min retention times. The hydrochloride was prepared as described for Compound D of Example 224.

MS: (M+H)⁺ 476

Analysis calculated for C₂₁H₂₃N₄O₂SBr • 1.2H₂O • 0.7 HCl.

Calc'd: C, 47.43; H, 4.85; N, 10.54; S, 6.03; Br, 15.03; Cl, 8.00.

Found: C, 47.71; H, 4.66; N, 9.71; S, 5.59; Br, 12.54; Cl, 8.14.

Example 379

5

N-[2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(2,3-dimethylbenzoyl)-1H-1,4-benzodiazepin-8-yl]cyclohexanecarboxamide, dihydrochloride.

10 **A. 8-Nitro-2,3,4,5-tetrahydro-4-Fmoc-1H-1,4-benzodiazepine**

FmocOSu (19.0 g, 56.4 mmol) was added to a -10°C solution of the dihydrochloride of Compound D of Example 22 (15.0 g, 56.4 mmol) and DIEA (19.6 ml, 113 mmol) in dichloromethane (100 ml). The mixture was stirred at 0°C for 2h, quenched with 10% NaHCO₃ (100 ml) and extracted with CH₂Cl₂ (2X100 ml). The combined organic extracts were washed with 1N HCl (2X100 ml). The organic fraction was washed with 10% NaHCO₃ (2X100 ml), dried (MgSO₄), filtered and concentrated under vacuum. The residue was triturated with ether and dried under vacuum to afford

20 Compound A as a white solid (15.6 g, 67%). MS: (M+H)⁺ 416

B. 8-Nitro-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-Fmoc-1H-1,4-benzodiazepine

4-Formylimidazole (7.16 g, 74.6 mmol) was added to a solution of Compound A (15.5 g, 37.3 mmol) with 4A molecular sieves (6 gm) in 1/1 CH₂Cl₂/AcOH (200 ml). The mixture was stirred at rt for 2h. Sodium triacetoxyborohydride (11.9 g, 56 mmol) was added portionwise over 15 minutes and the resulting solution was stirred for 3h. 4-Formylimidazole (1.10 g, 11.5 mmol) was added and the mixture was stirred for 1h. Sodium triacetoxyborohydride (2.39 g, 11.3 mmol) was added portionwise over 15

30

minutes and the resulting solution was stirred for 16h. The mixture was filtered and the filtrate was concentrated under vacuum. The residue was dissolved in CH_2Cl_2 (100 ml) and quenched with 10% NaHCO_3 (200 ml). The organic fraction was separated and the aqueous layer extracted with CH_2Cl_2 (2X100 ml). The combined organic fractions were dried (MgSO_4), filtered and concentrated under vacuum. The residue was purified by silica gel chromatography (eluting with CH_2Cl_2 , discarding all fractions and removing the product with 9/1 $\text{CHCl}_3/\text{MeOH}$) to afford Compound B (17.6 g, 95 %) as a glassy solid. $(\text{M}+\text{H})^+$ 496

C. N-[2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(2,3-dimethylbenzoyl)-1H-1,4-benzodiazepin-8-yl]cyclohexane-carboxamide, dihydrochloride

A solution of Compound B (12.0 g, 24.2 mmol) in DCE (70 ml) was added to 2-chlorotriylchloride polystyrene resin (13.9 g, 24.2 mmol, 1.74 mmol/g load, Advanced ChemTech) in a glass shaker flask, previously swollen with DCE (50 ml) at room temperature. DIEA (4.19 ml, 24.2 mmol) was added and the mixture was shaken at room temperature for 72h. The resin was filtered and washed with DCE (4X50 ml). The resin was washed with MeOH (4X50 ml), filtered and dried under vacuum to afford Compound B attached to resin via the imidazole group (23.1 g, 89%; loading 0.90 mmol/g based on nitrogen analysis) as orange beads. The resin (23.1g, 23.1 mmol) was swelled with DMF (50 ml) for 15 minutes. Piperidine (50 ml) was added and the mixture was shaken for 5h, filtered, washed with DMF (50 ml) and filtered. DMF (50 ml) was added and the mixture was shaken for 15 minutes. Piperidine (50 ml) was added and the mixture was shaken for 5h. The resin was filtered, washed and filtered with successive treatments of DMF (3X50 ml), CH_2Cl_2 (3X50 ml), and MeOH (3X80 ml) allowing 15 minutes to equilibrate resin after addition of each solvent. The resin was dried under vacuum to afford deprotected resin bound material (18.2 g 80%, loading 1.17 mmol/g based on nitrogen analysis) as orange beads. Resin (0.275 g, 0.322 mmol) was placed in a 25 ml Varian Bond Elut Reservoir tube fitted with a 20 mM Varian frit and polypropylene leuer tip stopcock. The tube was attached to Vac Elut SPS 24 on a Innova 2000 Platform Shaker. The resin was swelled with CH_2Cl_2 (2 ml) for 15 minutes. A 0.77 M DMF solution of 2, 3 dimethylbenzoic acid (1.25 ml) was added to the resin. A 0.92 M DMF solution of HOAT (1.04 ml) and a 0.46 M CH_2Cl_2 solution of DIC (2.08 ml)

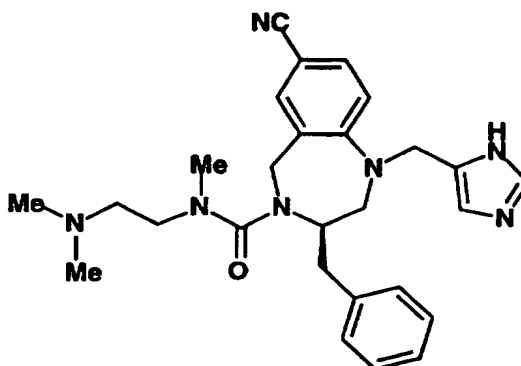
were added to the resin mixture. The platform shaker mixed the solid phase reaction @ 285 RPM for 16h. The tube was filtered and the resin was washed and filtered with successive treatments of DMF (3X5 ml), CH_2Cl_2 (3X5 ml), and MeOH (3X5 ml) allowing 15 minutes to equilibrate resin after addition of each solvent. The resin was again swelled with CH_2Cl_2 (2 ml) for 15 minutes. A 0.77 M DMF solution of 2, 3 dimethylbenzoic acid (1.25 ml) was added to the resin. A 0.92 M DMF solution of HOAT (1.04 ml) and a 0.46 M CH_2Cl_2 solution of DIC (2.08 ml) were added to the resin mixture. The platform shaker mixed the solid phase reaction @ 285 RPM for 16h. The tube was filtered and the resin was washed and filtered with successive treatments of DMF (3X5 ml), CH_2Cl_2 (3X5 ml), and MeOH (3X5 ml) allowing 15 minutes to equilibrate resin after addition of each solvent. This sequence of events afforded N4-acylated resin-bound material that was carried on to the next step. The resin was swelled with 1/1 DMF/ CH_2Cl_2 (2 ml) for 15 minutes. A 0.23 M solution of $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (0.222 g, 0.97 mmol), and TEA (0.672 ml, 4.83 mmol) in CH_2Cl_2 (4 ml) was added to the resin mixture. The resin mixture was shaken for 16h. The tube was filtered and the resin was washed and filtered with successive treatments of DMF (3X5 ml), CH_2Cl_2 (3X5 ml), and MeOH (3X5 ml) allowing 15 minutes to equilibrate resin after addition of each solvent. The resin was swelled with 1/1 DMF/ CH_2Cl_2 (2 ml) for 15 minutes and the entire procedure for this step was repeated two times. This sequence of events afforded 8-amino resin-bound material that was carried on to the next step. The resin was swelled with CH_2Cl_2 (2 ml) for 15 minutes. A 0.77 M DMF solution of cyclohexylcarboxylic acid (1.25 ml) was added to the resin. A 0.92 M DMF solution of HOAT (1.04 ml) and a 0.46 M CH_2Cl_2 solution of DIC (2.08 ml) were added. The platform shaker mixed the solid phase reaction @ 285 RPM for 16h. The tube was filtered and the resin was washed and filtered with successive treatments of DMF (3X5 ml), CH_2Cl_2 (3X5 ml), and MeOH (3X5 ml) allowing 15 minutes to equilibrate resin after addition of each solvent. The resin was again swelled with CH_2Cl_2 (2 ml) for 15 minutes. A 0.77 M DMF solution of cyclohexylcarboxylic acid (1.25 ml) was added to the resin. A 0.92 M DMF solution of HOAT (1.04 ml) and a 0.46 M CH_2Cl_2 solution of DIC (2.08 ml) were added to the resin mixture. The platform shaker mixed the solid phase reaction @ 285 RPM for 16h. The tube was filtered and the resin was washed and filtered with successive treatments of DMF (3X5 ml), CH_2Cl_2 (3X5 ml), and MeOH (4X5 ml) allowing 15 minutes to equilibrate resin after addition of each solvent. This sequence

of events afforded 8-acylated resin-bound material that was carried on to the next step. Resin was swelled with CH_2Cl_2 (4 ml) for 15 minutes.

Triethylsilane (0.51 ml, 3.2 mmol, 10 equiv) was added. The resin mixture was treated with TFA (4 ml) and the reaction was shaken for 1h. The filtrate was collected by vacuum filtration. The resin was again swelled with CH_2Cl_2 (4 ml) for 15 minutes. Triethylsilane (0.51 ml, 3.2 mmol, 10 equiv) was added. The resin mixture was treated with TFA (4 ml) and the reaction was shaken for 1h. The filtrate was collected by vacuum filtration. The combined filtrates were concentrated under vacuum. The residue was purified by preparative HPLC (gradient of aqueous methanol with 0.1% TFA) and appropriate fractions were collected and concentrated under vacuum. The residue was dissolved in CH_3CN (2 ml), treated with 1N HCl (1 ml) and concentrated under vacuum four times. The residue was dissolved in CH_3CN (2 ml), treated with 1N HCl (1 ml) and the solution was lyophilized to afford Example 379 (0.0075 g, 4% overall yield) as a glassy solid.

MS ($\text{M}+\text{H}$)⁺ 486

Example 380



(R)-7-Cyano-N-[2-(dimethylamino)ethyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-N-methyl-3-(phenylmethyl)-1H-1,4-benzodiazepine-4-carboxamide, trifluoroacetate (1:2).

A. (R)-7-Cyano-2,3,4,5-tetrahydro-4-(4-nitrophenyl-oxycarbonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine

To a solution of Compound C of Example 248 (200 mg, 0.76 mmol) in THF (20 mL) under argon was added 4-nitrophenylchloroformate (0.88 mL, 0.76 mmol). The solution was stirred for 8 hours, poured into aqueous hydrochloric acid (150 mL, 1N), extracted with ethyl acetate (2 x 150 mL),

dried (MgSO₄), and concentrated to an oil which was purified using flash chromatography (50 g silica, 2 : 1 hexane : ethyl acetate) to provide Compound A (230 mg, 70 %) as a clear oil.

5 **B. (R)-7-Cyano-N-[2-(dimethylamino)ethyl]-2,3,4,5-tetrahydro-N-methyl-3-(phenylmethyl)-1H-1,4-benzodiazepine-4-carboxamide**

 A solution of Compound A (110 mg, 0.26 mmol), in N,N,N'-trimethylethylene diamine (2 mL) was heated in a sealed pressure tube at
10 110°C for 18 hours. After cooling to room temperature, the solution was poured into aqueous sodium hydroxide (100 mL, 1N), extracted with ethyl acetate (2 x 150 mL), dried (MgSO₄) and concentrated under vacuum to afford crude Compound B as a brown paste (yield >100 %).

15 **C. (R)-7-Cyano-N-[2-(dimethylamino)ethyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-N-methyl-3-(phenylmethyl)-1H-1,4-benzodiazepine-4-carboxamide, trifluoroacetate (1:2)**

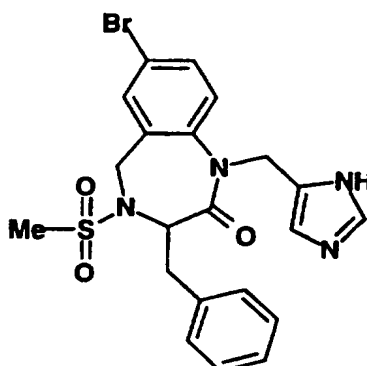
 A solution of Compound B (140 mg, 0.35 mmol), 4-formyl imidazole
20 (68 mg, 0.7 mmol), dichloroethane (2 mL) and acetic acid (2 mL) was stirred at room temperature for 30 min and sodium triacetoxyborohydride (150 mg, 0.7 mmol) was added. The solution was heated to 60°C, stirred for 18 hour, and additional portions of 4-formyl imidazole and sodium
25 triacetoxyborohydride were added (0.2 mmol each, 4 portions over 8 hours); the mixture was diluted with ethyl acetate (20 mL) and ammonium hydroxide (5 ml, conc), and stirred for an additional 30 min. The mixture was extracted with ethyl acetate (2 x 25 mL) and the combined organic extracts were washed with aqueous sodium bicarbonate (25 ml, saturated solution), and then ammonium chloride (25 mL, sat aqueous solution), dried (Na₂SO₄),
30 and concentrated in vacuo to a semi-solid. The crude was purified by preparative HPLC (aqueous methanol gradient containing 0.1% TFA, C-18 column) and lyophilized to provide Compound C as a white solid (80 mg, 48%).

MS: (M+H)⁺ 471

35 Analysis calculated for C₂₇H₃₃N₇O 1.1H₂O . 2.1 TFA.

Calc'd: C, 51.27; H, 5.14; N, 13.42; F, 16.38.

Found: C, 51.60; H, 4.93; N, 13.47; F, 16.28.

Example 381

5

7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methanesulfonyl)-2-oxo-3-(phenylmethyl)-1H-1,4-benzodiazepin , trifluoroacetate.

10 **A. N-((2-Nitrophenyl)-methyl)-phenylalanine methyl ester**

To a solution of 2-nitrobenzaldehyde (5g, 33 mmol) in acetic acid (150 mL) was added D,L phenylalanine-O-methyl ester (8.54 g, 40 mmol) and then sodium acetate (3.5 g, 43 mmol). Sodium triacetoxyborohydride (9.09 g, 43 mmol) was slowly added and the mixture was heated to 80°C for
 15 four hours, cooled to room temperature, concentrated under vacuum to a paste (~20 mL) and dissolved in ethyl acetate (100 mL). The solution was neutralized with saturated sodium carbonate and extracted with ethyl acetate (3 x 200 mL). The combined organic layers were dried (MgSO₄), and concentrated to provide Compound A as a brown oil (11.25 g, > 100 %).

20

B. N-((2-Nitrophenyl)-methyl)-N-(methanesulfonyl)-phenylalanine methyl ester

To a solution of Compound A (1.12 g, 3.5 mmol) in pyridine (10 mL) under argon in an ice bath was slowly added methanesulfonyl chloride (1.08 mL, 14.0 mmol). The solution was warmed to room temperature, poured into
 25 aqueous hydrochloric acid (250 mL, 1N), extracted with ethyl acetate (2 x 200 mL) and the combined organic layers dried (MgSO₄) and concentrated. The oil was purified by flash chromatography (4:1 hexane:ethyl acetate) to provide Compound B (660 mg, 48%) as a clear oil.

C. N-((2-Aminophenyl)-methyl)-N-(methanesulfonyl)-phenylalanine methyl ester

A mixture of Compound B (660 mg, 1.68 mmol), tin (II) chloride (1.52 g, 6.7 mmol) and ethyl acetate (75 mL) was stirred at room temperature for 18 hours and quenched with aqueous and then solid potassium carbonate (5 mL, then 5 gms). The mixture was filtered, the filtrate partitioned and the organic phase dried (MgSO₄), concentrated in vacuum, and purified using flash chromatography (3:1 hexane : ethyl acetate) to provide Compound C (315 mg, 52 %) as a clear oil.

D. N-((2-Amino-5-bromophenyl)-methyl)-N-(methanesulfonyl)-phenylalanine methyl ester

Compound D was prepared as a white solid in 60% yield from Compound C as described for Compound A of Example 262 except that the product was purified by crystallization from methanol.

E. N-[[2-(((Imidazol-4-yl)-methyl)-amino)-phenyl]-methyl]-N-(methanesulfonyl)-phenylalanine methyl ester

Compound E was prepared as a semi-solid in 100% yield from Compound D as described for Compound D of Example 1, with stirring for 4 hours and with the crude free base carried on directly.

F. N-[[2-(((Imidazol-4-yl)-methyl)-amino)-phenyl]-methyl]-N-(methanesulfonyl)-phenylalanine

A solution of Compound E (200 mg, 0.38 mmol) and LiOH (80 mg, 2 mmol) in THF (6 mL), methanol (1 mL) and water (1 mL) was stirred at room temperature for 1 hour, concentrated under vacuum to 2 mL and poured into aqueous hydrochloric acid (20 mL, aqueous). The mixture was extracted with ethyl acetate (2 x 50 mL) and the combined organic layers were dried (MgSO₄), and concentrated to provide Compound F (150 mg, 78 %) as a clear oil.

G. 7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-2-oxo-3-(phenylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate

A mixture of Compound F (150 mg, 0.29 mmol), DMF (3 mL), DIEA (0.66 mL, 0.725 mmol), and BOP (193 mg, 0.43 mmol) was stirred at room temperature for 3 hours. The mixture was partitioned between sodium carbonate (100 mL, sat soln) and ethyl acetate (100 mL), the aqueous phase was extracted with ethyl acetate (2 x 50 mL) and the combined organic layers were dried (MgSO₄) and concentrated. The residue was purified by preparative HPLC (aqueous methanol gradient containing 0.1% trifluoroacetic acid, C-18 column) and lyophilized to provide Compound G as a white solid (65 mg, 46 %).

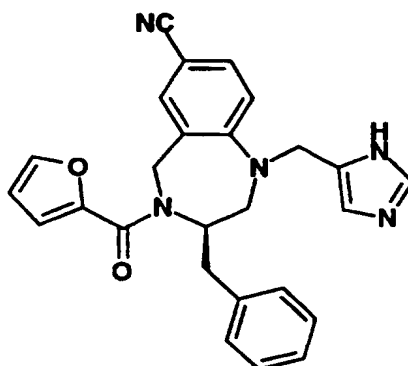
MS: (M+H)⁺ 490

Analysis calculated for C₂₁H₂₁N₄O₃ • 1.1H₂O • 1.0 TFA.

Calc'd: C, 44.33; H, 3.91; N, 8.99; S, 5.14; Br, 12.82.

Found: C, 44.29; H, 3.59; N, 8.74; S, 5.05; Br, 12.78.

Example 382



(R)-7-Cyano-4-(2-furanylcarbonyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate (1:1).

A. (R)-7-Cyano-4-(2-furanylcarbonyl)-2,3,4,5-tetrahydro-3-(phenylmethyl)-1H-1,4-benzodiazepine

Compound A was prepared as a oil in 100% yield from Compound C of Example 248 and furan-2-carboxylic acid as described for Compound G

of Example 381, with stirring for 18 hours, workup with citric acid, and no purification.

5 **B. (R)-7-Cyano-4-(α -furanylcarbonyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate (1:1)**

Compound B was prepared as a white solid in 7% yield from Compound A as described for Compound C of Example 380.

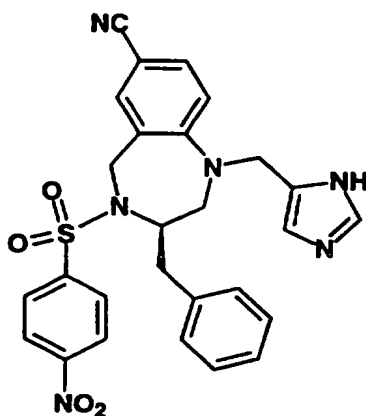
MS: (M+H)⁺ 438

10 Analysis calculated for C₂₆H₂₃N₅O₂ • 2.0 H₂O • 1.0 TFA.

Calc'd: C, 57.24; H, 4.80; N, 11.92.

Found: C, 57.22; H, 4.26; N, 11.74.

Example 383



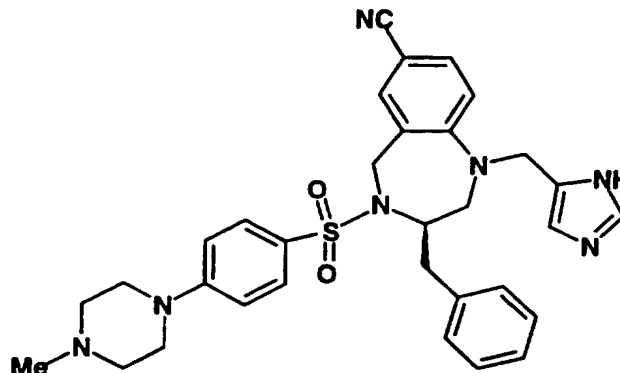
(R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[(4-nitrophenyl)sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate.

20

Example 383 was prepared as a white solid in 3% yield from 4-nitrobenzene sulfonylchloride and Compound C of Example 248 by the following sequence: Compound C of Example 350, except that the reaction was run at room temperature and no purification was performed; Compound

25

MS: (M+H)⁺ 529

Example 384

5 **(R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[[4-(4-methyl-1-piperazinyl)phenyl]sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate.**

10 **A. (R)-7-Cyano-2,3,4,5-tetrahydro-4-[[4-(4-methyl-1-piperazinyl)phenyl]sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine**

To a mixture of (R)-7-cyano-2,3,4,5-tetrahydro-4-[(4-fluorophenyl)sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine (200 mg, 0.48 mmol, prepared as described in Example 291) in DMF (2 mL) was added N-methylpiperazine (2 mL). The solution was heated to 110°C and stirred for six hours, poured into aqueous hydrochloric acid (150 mL, 1 M) and extracted with ethyl acetate (2 x 100 mL). The organic layers were combined, dried (MgSO₄), concentrated and the residue crystallized from dichloromethane to provide Compound A (50 mg, 21 %) as a grey solid.

20 **B. (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[[4-(4-methyl-1-piperazinyl)phenyl]sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate**

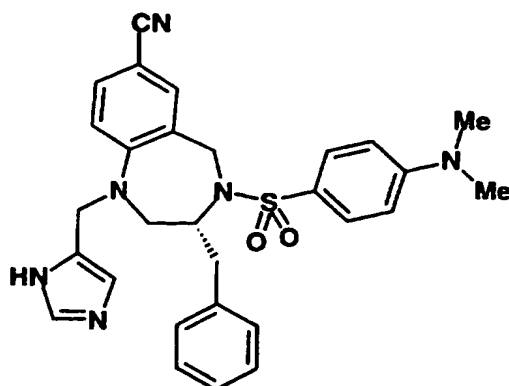
Compound B was prepared as a white solid in 65% yield from Compound A as described for Compound C of Example 380, with stirring at room temperature.

MS: (M+H)⁺ 581

Analysis calculated for C₃₂H₃₅N₇O₃S • 2.0H₂O • 2.0 TFA.

Calc'd: C, 51.12; H, 4.89; N, 11.59; S, 3.79.

Found: C, 50.83; H, 4.68; N, 11.43; S, 4.47.

Example 385

5 **(R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[[[4-(dimethylamino)phenyl]sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate.**

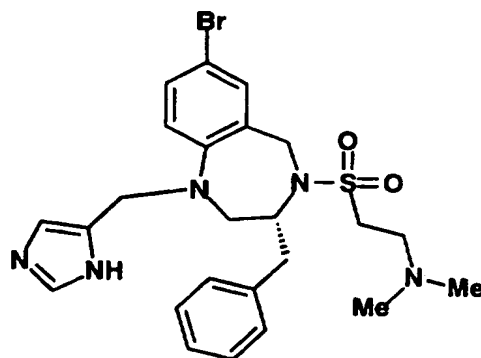
10 **A. (R)-7-Cyano-2,3,4,5-tetrahydro-4-[[[4-(dimethylamino)phenyl]sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine**

A solution of (R)-7-cyano-2,3,4,5-tetrahydro-4-[[[4-fluorophenyl]sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine (200 mg, 0.48 mmol, prepared as described in Example 291) in dimethylamine (2 mL, 2 M in THF) was stirred at 60°C in a sealed pressure tube for 24 hours. Additional dimethylamine (4 mL, 2 M in THF) was added and the solution was stirred for an additional 6 hours. The reaction was concentrated to a paste under vacuum and the residue crystallized from methanol to provide Compound A (50 mg, 25%) as a grey solid.

20

B. (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[[[4-(dimethylamino)phenyl]sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate

Compound B was prepared as a white solid in 43% yield from Compound A as described for Compound C of Example 380. Analysis calculated for Calcd for $C_{29}H_{30}N_6O_2S \cdot 1.3 H_2O \cdot 0.9 TFA$.
Calc'd: C, 56.68; H, 5.17; N, 12.88; S, 4.91; F, 7.80.
Found: C, 56.36; H, 5.07; N, 12.51; S, 5.39; F, 7.78.

Example 386

- 5 **(R)-7-Bromo-4-[[2-(dimethylamino)ethyl]sulfonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4H-1,4-benzodiazepine, dihydrochloride.**

10 **A. (R)-7-Bromo-4-[ethenylsulfonyl]-2,3,4,5-tetrahydro-3-(phenylmethyl)-4H-1,4-benzodiazepine**

To a solution of Compound B of Example 224 (10 g, 31.5 mmol) in dichloromethane (120 mL) at 0°C was added dropwise a solution of 2-chloroethanesulfonyl chloride (3.2 mL, 30 mmol) in dichloromethane (10 mL). DIEA (5.2 mL, 30 mmol) was added dropwise. After 15 min, 2-chloroethanesulfonyl chloride (1.5 mL, 15 mmol) followed by DIEA (10.4 mL, 60 mmol) were added. The mixture was allowed to warm to rt and poured into water (80 mL). The organic layer was separated, washed with 1N HCl and saturated aqueous NaHCO₃ (80 mL each), dried (MgSO₄) and concentrated in vacuo to afford Compound A as a yellowish foamy solid (15.2 g). MS: (M+H)⁺ = 406⁺

25 **B. (R)-7-Bromo-4-[[2-(dimethylamino)ethyl]sulfonyl]-2,3,4,5-tetrahydro-3-(phenylmethyl)-4H-1,4-benzodiazepine**

A flask was charged with Compound A (7g) and a THF solution of dimethylamine (2M, 20 mL). The flask was stoppered and the mixture was stirred 18 hr, concentrated and purified by silica gel column chromatography eluting with 20% acetone in chloroform to afford Compound B (48% from Compound B of Example 224).

C. (R)-7-Bromo-4-[[2-(dimethylamino)ethyl]sulfonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4H-1,4-benzodiazepine, dihydrochloride

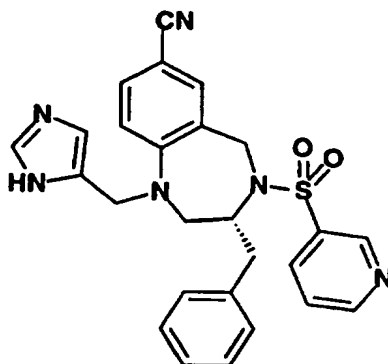
To a solution of Compound B (5.3 g, 11.7 mmol) in dichloromethane (100 mL) were added acetic acid (15 mL) and 4-formylimidazole (1.15 g, 12 mmol). After 10 min, sodium triacetoxymethylborohydride (2.54 g, 12 mmol) was added. After 3 hr, 4-formylimidazole (0.5 g, 5.8 mmol) and borohydride (1.2 g, 5.5 mmol) were added. After 18 hr, aldehyde (0.5 g) and borohydride (1.2 g) were added. After 5 hr, the mixture was concentrated. Aqueous ammonia (100 mL) and chloroform (100 mL) were added to the residue and the mixture was stirred vigorously for 0.5 hr. The two layers were separated and the organic layer was washed again with aqueous ammonia (100 mL). The combined aqueous layer was extracted with chloroform (100 mL), the two organic extracts were combined, dried (K_2CO_3), and concentrated. The residue was purified by flash silica gel column chromatography (step gradient of 5% and 10% MeOH in chloroform) to afford a solid which was dissolved in dichloromethane (50 mL) and HCl gas was bubbled through the solution. The mixture was concentrated in vacuo to afford a solid which was dissolved in water and lyophilized to afford Compound C (5.2 g, 73 %).

MS: $(M+H)^+$ 532

Analysis calculated for $C_{24}H_{30}BrN_5O_2S \cdot 2HCl$.

Calc'd: C, 47.61; H, 5.33; N, 11.57.

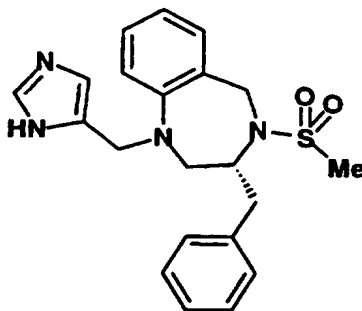
Found: C, 47.36; H, 5.45; N, 11.34.

Example 387

5 **(R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(3-pyridinylsulfonyl)-1H-1,4-benzodiazepine, trihydrochloride.**

Example 387 was prepared as a yellow solid in 15% yield from
Compound C of Example 248 and 3-pyridinesulfonyl chloride as described
10 for Example 284.

MS: (M+H)⁺ 485

Example 388

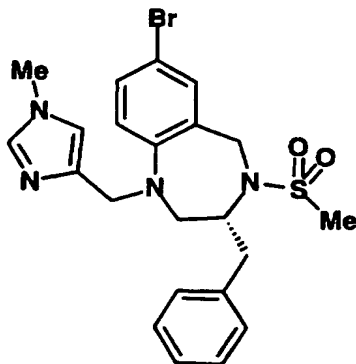
15 **2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.**

20 BuLi (1.0 M in THF, 5 mmol) was added to a solution at -78°C of the free base of Example 224 (0.104 g, 0.19 mmol) in THF (10 mL). After 5 min., H₂O/THF (1:1, 10 mL) was added. The solution was saturated with NaCl. The aqueous layer was extracted with CH₂Cl₂. The combined organic

phases were dried over Na_2SO_4 . Evaporation of solvent gave a solid which was purified by reverse phase preparative HPLC (gradient of aqueous methanol with 0.1% TFA) and converted into its HCl salt to afford 25 mg (30%) of Example 388 as a yellow solid.

5 MS: $(\text{M}+\text{H})^+$ 397

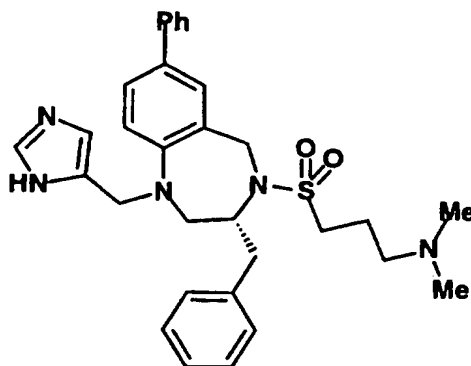
Example 389



10 **(R)-7-Bromo-2,3,4,5-tetrahydro-1-[(1-methyl-1H-imidazol-4-yl)methyl]-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.**

NaH (60% in mineral oil, 1 g) was added to a solution at -10°C of the free base of Example 224 (0.23 g, 0.19 mmol) in DMF/THF (1:1, 10 mL). After 20 min., MeI (0.7 mL) was added. The mixture was stirred at -5°C for 1 hr, quenched with MeOH (5 mL) and diluted with CH_2Cl_2 (20 mL). The organic phase was washed with 2.5% NaOH. The organic phase was dried over Na_2SO_4 . Evaporation of solvent gave a solid which was purified by reverse phase preparative HPLC (gradient of aqueous methanol with 0.1% TFA) followed by preparative TLC (8% MeOH, 2% $i\text{Pr}_2\text{NH}$ in CH_2Cl_2) to provide 10 mg of Example 389 (10%) as a white solid.

20 MS: $(\text{M}+\text{H})^+$ 491

Example 390

5 **(R)-4-[[3-(Dimethylamino)propyl]sulfonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.**

A. (R)-4-[[3-Chloropropyl]sulfonyl]-2,3,4,5-tetrahydro-7-phenyl-3-(phenylmethyl)-1H-1,4-benzodiazepine

10 To a solution of Compound D of Example 226 (4.7 g, 15 mmol) and DIEA (7 mL, 40 mmol) in CH₂Cl₂ (40 mL) at 0°C was added slowly 3-chloropropanesulfonyl chloride (2 mL, 16 mmol) in CH₂Cl₂ (5 mL). After 2 hrs, the solvent was evaporated. The residue was dissolved in CH₂Cl₂ (20 mL) and the solution was washed with 1N NaOH (2x 50 mL), dried and
15 evaporated to provide Compound A as an oil (5.5 g).

B. (R)-4-[[3-Chloropropyl]sulfonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-3-(phenylmethyl)-1H-1,4-benzodiazepine

20 A solution of Compound A (5.5 g) and 4-formylimidazole (3 g, 30 mmol) in AcOH/ CH₂Cl₂ (1:5 , 300 mL) was stirred for 1 hr. NaBH(OAc)₃ (total 9 g, 42 mmol) was added (3 g every 4 hrs) and the solution was stirred for 12hr. The solvent was evaporated and the residue was treated with 3% NaOH (50 mL). The solid was filtered and washed with water (5x100 mL)
25 and dried to give Compound B (7.5 g).

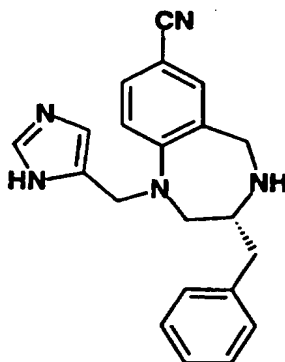
C. (R)-4-[[3-(Dimethylamino)propyl]sulfonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride

A solution of Compound B (7 g) and dimethylamine (2.0 M in THF, 75 mL, 150 mmol) in DMF (150 mL) was warmed to 80°C (sealed tube) for 30 hr. The DMF was removed. The residue was passed through a short silica gel column (5% MeOH, 0.5% NH₄OH in CH₂Cl₂). The eluant was evaporated and the residue was purified by reverse phase preparative HPLC (gradient of aqueous methanol with 0.1% TFA) and converted to the HCl salt to provide Compound C as an off white solid (5.0 g, 60% from Compound D of Example 226)

MS: (M+H)⁺ 544

¹H-NMR (CD₃OD, 300Mhz) δ: 1.80 (m, 2H), 2.8 (m, 2H), 3.0 (m, 4H), 3.20 (m, 2H), 3.60 (m, 2H), 4.30 (m, 1H), 4.6 (m, 2H), 6.8 (d, 7Hz, 1H), 7.1 to 7.6 (m, 13H), 8.92 (s, 1H).

Example 391

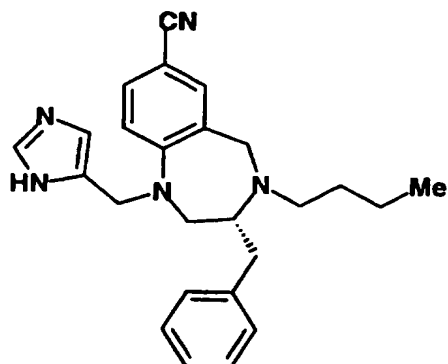


(R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, trihydrochloride.

Example 391 is Compound C of Example 280.
MS(M+H)⁺ 244.

Example 392

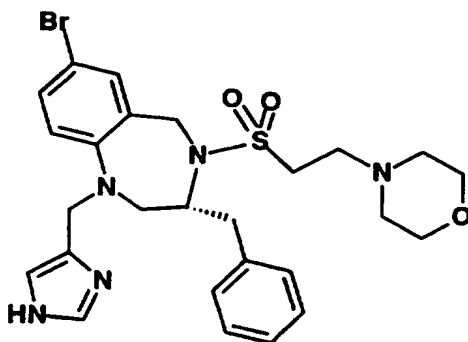
5



4-Butyl-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, trihydrochloride.

10 A solution of Example 391 (0.23 g, 0.7 mmol) and butyraldehyde (1 g, 14 mmol) in 1:4 AcOH/CH₂Cl₂ (25 mL) was stirred at rt for 1 hr. NaBH(OAc)₃ (3.0 g, 14 mmol) was added and stirring was continued for 14 hrs. The reaction was quenched with conc. NH₄OH and diluted with 10% iPrOH in CH₂Cl₂ (50 mL). The organic phase was washed with 1N NaOH
15 (2x20 mL), dried over Na₂SO₄ and evaporated to give a yellow solid (0.4 g) which was purified by reverse phase preparative HPLC (gradient of aqueous methanol with 0.1% TFA) and converted to the HCl salt by lyophilizing with 1N HCl to give Example 392 as a yellow solid (45 mg, 12%).
MS (M+H)⁺ 400.

20

Example 393

(R)-7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[[2-(4-morpholinyl)ethyl]sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.

A. (R)-7-Bromo-2,3,4,5-tetrahydro-4-[[2-(4-morpholinyl)ethyl]sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine

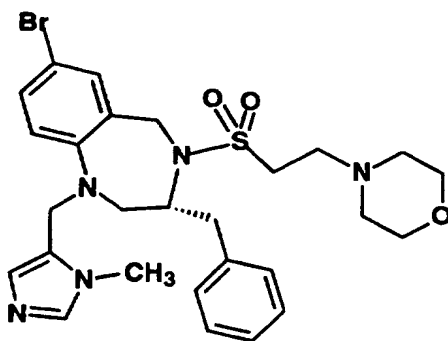
To a solution of Compound A of Example 386 (0.23 g, 0.34 mmol, 61% pure) in THF (1.5 mL) at rt was added morpholine (0.2 mL). The mixture was stirred 16 hr, diluted with ethyl acetate (15 mL), washed with water and brine (15 mL each), dried and concentrated in vacuo. The residue was purified with flash silica gel column chromatography eluting with 20% acetone in chloroform to afford Compound A as a white solid (130 mg, 77%).

B. (R)-7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[[2-(4-morpholinyl)ethyl]sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride

A mixture of Compound A (0.060 g, 0.12 mmol), 4-formylimidazole (0.011 g, 0.12 mmol), 3A sieves and AcOH (0.2 mL) in dichloroethane (0.3 mL) was stirred at rt, under argon. After 2 hr, sodium triacetoxyborohydride (0.025 g, 0.12 mmol) was added. After stirring for 16 hr, the mixture was diluted with CHCl₃ (10 mL), NH₄OH (5 mL) and NaHCO₃ (5 mL), and stirred for 30 min. The layers were separated and the aqueous layer was extracted with CHCl₃ (2 x 20 mL). The combined organic extracts were washed with NaHCO₃, water, brine (3 x 10 mL each), dried over MgSO₄, filtered and concentrated. The residue was purified by reverse phase preparative HPLC (gradient of aqueous methanol with 0.1% TFA). The appropriate fractions

were concentrated under vacuum. The residue was evaporated from MeOH (1 mL) and 1N HCl (1 mL) 3 times. The residue was dissolved in water and lyophilized to afford Compound B as a light yellow solid (0.019 g, 28 %). MS (M+H)⁺ 574.

5

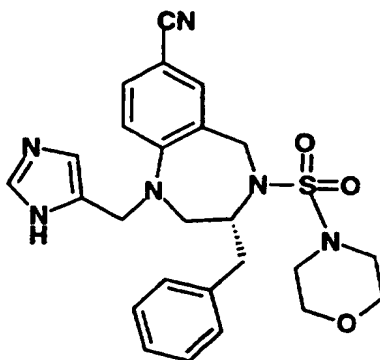
Example 394

- 10 **(R)-7-Bromo-2,3,4,5-tetrahydro-1-[(1-methyl-1H-imidazol-5-yl)methyl]-4-[[2-(4-morpholinyl)ethyl]sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.**

Example 394 was prepared as a light yellow solid in 23% yield from Compound A of Example 393 and N-methyl-5-formylimidazole as described for Compound B of Example 393, with stirring under reflux for 7 hours before addition of hydride, cooling to rt, adding hydride, and stirring 16 hours after addition of hydride.

MS (M+H)⁺ 588.

20

Example 395

(R)-7-Cyano-1-(1H-imidazol-4-ylmethyl)-4-(4-morpholinylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.

A. (R)-7-Cyano-4-(4-morpholinylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine

To a solution of Compound C of Example 248 (263 mg, 1 mmol) in acetonitrile (2 mL) at rt under argon were added morpholinesulfamoyl chloride (371 mg, 2 mmol) and DIEA (0.35 mL, 2 mmol). The resulting brown mixture was stirred for 65 hr and concentrated, and the residue was partitioned between 1N HCl and chloroform (10 mL each). The organic layer was separated, washed with saturated NaHCO_3 , dried (MgSO_4) and concentrated. The residue was purified by flash silica gel column eluting with a step gradient of 40% and 50% EtOAc in hexanes to afford Compound A (95 mg, 71%) as a pale yellow solid.

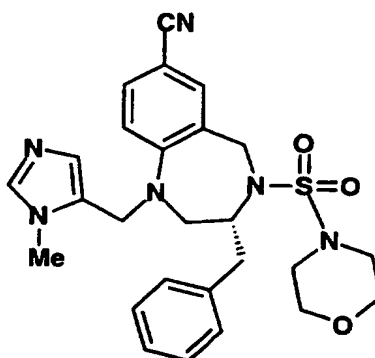
MS ($\text{M}+\text{H}$)⁺ = 413

B. (R)-7-Cyano-1-(1H-imidazol-4-ylmethyl)-4-(4-morpholinylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride

To a solution of Compound A (206 mg, 0.5 mmol) in 1,2-dichloroethane (2 mL) at RT under argon were added 4-formylimidazole (380 mg, 4 mmol), HOAc (0.5 mL) and 3A sieves. The mixture was warmed to 50°C and sodium triacetoxyborohydride (330 mg, 1.5 mmol) was added. After 18 hr, more hydride (212 mg, 1 mmol) was added. After 5 more hrs, the mixture was cooled to RT, filtered through celite and carefully treated with

30% NH_4OH (10 mL) and chloroform (10 mL). The mixture was vigorously stirred for 1 hr, the organic layer was separated and washed with 15% ammonia solution (15 mL), dried (K_2CO_3) and concentrated. The brown oil obtained was purified by silica gel column chromatography eluting with 5% MeOH in chloroform to afford the free base of Compound B (150 mg, 61%) as a white solid. 26 mg of this solid was treated with 1N HCl in ether followed by concentration in vacuo to afford Compound B (28 mg). MS $(\text{M}+\text{H})^+ = 493$; $(\text{M}-\text{H})^- = 491$.

10

Example 396

(R)-7-Cyano-1-[(1-methyl-1H-imidazol-5-yl)methyl]-4-[(4-morpholinyl)sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.

A. (R)-7-Cyano-1-[(1-triphenylmethyl-1H-imidazol-4-yl)methyl]-4-[(4-morpholinyl)sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine

To a solution of the free base of Example 395 (120 mg, 0.24 mmol) in acetonitrile (2 mL) at RT under argon were added trityl chloride (83 mg, 0.3 mmol) and DIEA (0.053 mL, 0.3 mmol). The mixture was refluxed for 4 hr, cooled to RT and concentrated. The residue was dissolved in chloroform (15 mL) and washed with water and saturated NaHCO_3 (15 mL each). The organic layer was dried (MgSO_4), and concentrated. The residue was washed with warm hexanes (2 x 5 mL) to afford Compound A (178 mg, 100%) as a pale yellow solid.

B. (R)-7-Cyano-1-[(1-methyl-1H-imidazol-5-yl)methyl]-4-[(4-morpholinyl)sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride

To a solution of Compound A (170 mg, 0.23 mmol) in dichloromethane (2 mL) at -78°C under argon was added methyl triflate (0.027 mL, 0.24 mmol). After 1 hr, the cold bath was removed and replaced with ice bath (0°C). After 2 hr, 50% aqueous acetic acid (2 mL) was added and the mixture was refluxed 40 min. Chloroform and saturated NaHCO₃ (10 mL each) were added and the mixture was stirred carefully until effervescence subsided. Solid K₂CO₃ was added carefully until pH 11 of the aqueous layer was achieved. The organic layer was separated, dried (K₂CO₃) and concentrated in vacuo. The solid residue was washed with warm hexanes and ether (2 X 10 mL each). The solid was dissolved in EtOAc (5 mL) and 1N HCl in ether (2 mL) was added. The precipitate was collected and washed with EtOAc (3 X 5 mL). The solid was dried in vacuo at 40°C to afford Compound B as a pale yellow solid (110 mg, 84%).

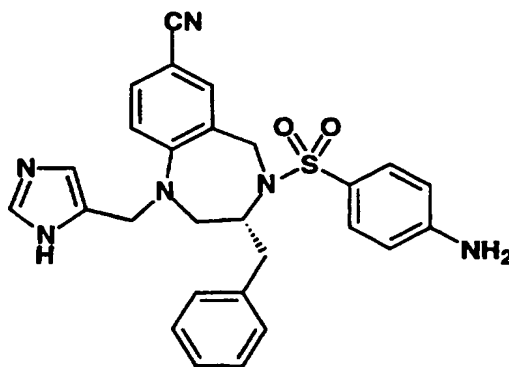
MS: (M+H)⁺ = 507.

Analysis calculated for C₂₆H₃₀N₆O₃S • 1.7 HCl.

Calc'd: C, 54.75; H, 5.61; N, 14.73.

Found: C, 55.15; H, 5.68; N, 14.29.

Example 397

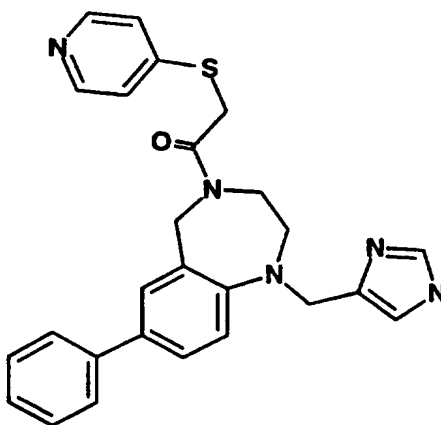


25

(R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[(4-aminophenyl)sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, hydrochloride.

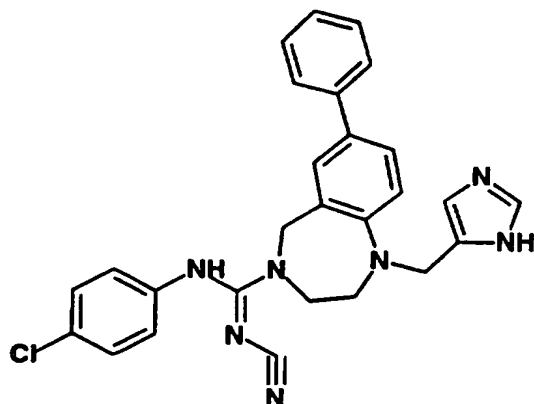
To a stirred solution of the free base of Example 383 (5 mg) in ethyl acetate was added SnCl₂. The solution was stirred at room temperature for 18h. NH₄OH was added, followed by MgSO₄. The suspension was filtered, and the filtrate was concentrated in vacuo. The residue was dissolved in methanol, 1N HCl in ether was added. The solvent was removed to give 2.0 mg Example 397 (40%) as a yellow solid .

Example 398



2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[(4-pyridylthio)acetyl]-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride.

Example 398 was prepared from Compound B of Example 33 as described for Examples 101-201.
MS (M+H)⁺ 456.

Exempl 399

5 **N-(4-Chlorophenyl)-N'-cyano-1,2,3,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4H-1,4-benzodiazepine-4-imidamide, monohydrochloride.**

10 **A. N-(4-Chlorophenyl)-N'-cyano-1,2,3,5-tetrahydro-7-phenyl-4H-1,4-benzodiazepine-4-imidamide**

To a stirred solution of Compound B of Example 12 (110 mg, 0.5 mmol) in DMF was added sequentially N-(4-chlorophenyl)-N'-cyanothiourea (130 mg, 0.62 mmol), and EDC (120 mg, 0.61 mmol). The solution was stirred at room temperature for 18 h and partitioned between ethyl acetate and sat'd NH₄Cl solution. The organic layer was separated, washed with saturated NaHCO₃ solution and brine, dried, and concentrated. The residue was crystalized from MeOH to give Compound A as a solid (150 mg, 75%). MS: 402 (M+H).

20 **B. N-(4-Chlorophenyl)-N'-cyano-1,2,3,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4H-1,4-benzodiazepine-4-imidamide, monohydrochloride**

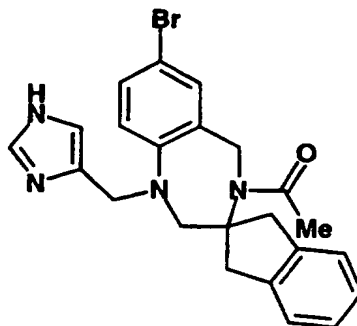
Compound B was prepared as a solid in 78% yield from Compound A as described for Compound D of Example 1. MS: 482 (M+H)

Analysis calculated for C₂₇H₂₃N₇Cl•2.2HCl•2H₂O.

Calc'd: C, 54.30; H, 4.93; N, 16.42; Cl, 18.99.

Found: C, 54.57; H, 4.90; N, 16.76; Cl, 18.90.

Example 400



5

4-Acetyl-7-bromo-1,2,4,5,1',3'-hexahydro-1-(1H-imidazol-4-ylmethyl)spiro[3H-1,4-benzodiazepine-3,2'-[2H]indene], dihydrochloride.

10

A. N-[(2-Amino-5-bromophenyl)carbonyl]-2-amino-2-indanecarboxylic acid

A solution of 2-amino-2-indanecarboxylic acid (680 mg, 4.15 mmol), bromoisatoic anhydride (1.0 g, 4.15 mmol) and pyridine•HCl (2.0 g, 1.72 mmol) in pyridine (30 mL) was refluxed for 4h, cooled and concentrated. The residue was partitioned between water (200 mL) and ethyl acetate (200mL). The organic layer was washed with water (3X100mL), brine (50 mL), dried (MgSO₄) and concentrated to yield compound Compound A as a yellowish glass (350 mg, 22 %). MS (M+H)⁺ 375.

20

B. 7-Bromo-1,2,4,5,1',3'-hexahydro-spiro[3H-1,4-benzodiazepin-2,5-dione-3,2'-[2H]indene]

A solution of Compound A (350 mg, 0.93 mmol), EDC (203 mg, 1.02 mmol), DIEA (0.35 mL, 2.00 mmol) and HOBt (135 mg, 1.00 mmol) in DMF (10 mL) was stirred for 16 h and poured into water (100 mL). The mixture was extracted with ethyl acetate (2X50 mL). The combined ethyl acetate layers were washed with water (3X100 mL), brine (100 mL), dried (MgSO₄) and concentrated to yield compound Compound B as a brown glass (150 mg, 45 %). MS (M+H)⁺ 358.

30

C. 7-Bromo-1,2,4,5,1',3'-hexahydro-spiro[3H-1,4-benzodiazepine-3,2'-[2H]indene]

To a solution of Compound B (150 mg, 0.42 mmol) in THF (10 mL) was added borane (1M in THF, 3 mL, 3 mmol). The solution was refluxed for 3h and cooled to room temperature. Methanol (5 mL) was added and the solution was concentrated. 5N HCl (10 mL) was added and the mixture was refluxed for 4h, cooled to room temperature, neutralized to pH 6 with 50% NaOH and extracted with methylene chloride (3X50 mL). The combined organic layers were washed with brine (30 mL), dried (MgSO₄) and concentrated to yield compound C as a slightly yellow glass (70 mg, 50%). MS (M+H)⁺ 330.

D. 4-Acetyl-7-bromo-1,2,4,5,1',3'-hexahydro-spiro[3H-1,4-benzodiazepine-3,2'-[2H]indene]

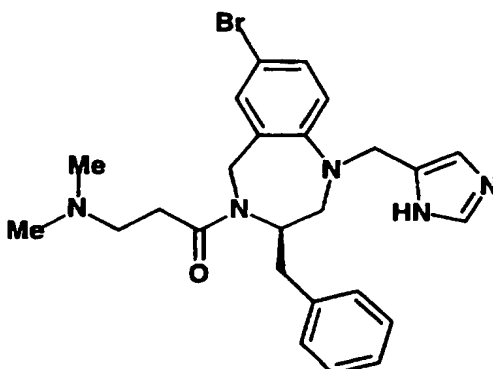
Compound C (70 mg, 0.21 mmol) was dissolved in THF (5 mL) and DIEA (37 μ L, 0.21 mmol) was added followed by acetyl chloride (15 μ L, 0.21 mmol). The solution was stirred for 30 min, concentrated, dissolved in ethyl acetate (50 mL) and washed with water (3X20 mL). The organic layer was dried (MgSO₄) and concentrated to yield Compound D as a light brown glass.

E. 4-Acetyl-7-bromo-1,2,4,5,1',3'-hexahydro-1-(1H-imidazol-4-ylmethyl)spiro[3H-1,4-benzodiazepine-3,2'-[2H]indene], dihydrochloride

Compound D and 4-formylimidazole were dissolved in 1,2-DCE (5 mL) and acetic acid (0.5 mL) was added followed by sodium triacetoxyborohydride. The mixture was stirred at 50°C for 2h and saturated NaHCO₃ (5 mL) was added. The mixture was concentrated and the residue was partitioned between water (20 mL) and ethyl acetate (20mL). The organic layer was washed with water (10mL), brine (10 mL), dried (MgSO₄), concentrated and purified by RP preparative HPLC (gradient of aqueous methanol with 0.1% TFA). Fractions containing the desired product were combined, concentrated and lyophilized. This lyophilate was dissolved in methanol (0.5 mL) and 1N HCl (5mL). This mixture was concentrated and lyophilized. This procedure was repeated to provide Compound E as a white solid (12 mg, 13%)

MS (M+H)+ 451.

Exempl 401



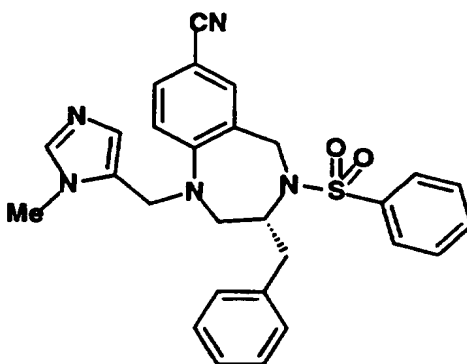
5

7-Bromo-4-[3-(dimethylamino)-1-oxopropyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate (1:1).

10 Example 401 was prepared as a white solid in 6% overall yield from Compound B of Example 224 by the following sequence: EDC/HOBt mediated coupling of acrylic acid in DMF, with purification by flash chromatography; Compound D of Example 232; Compound D of Example 224.

15 MS: (M + H)+ 466.

Example 402

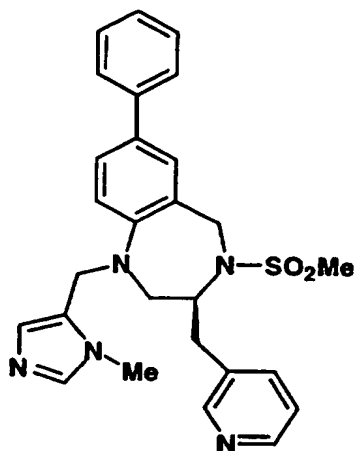


20 **(R)-2,3,4,5-Tetrahydro-1-(1-methyl-1H-imidazol-5-ylmethyl)-4-(phenylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine-7-carbonitril , monohydrochlorid .**

A solution of (R)-7-cyano-2,3,4,5-tetrahydro-1-[[[(1,1-dimethyl thoxy)-carbonyl]-1H-imidazol-4-yl)methyl]-4-(phenylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine (0.23 g, 0.4 mmol, prepared from Example 312 as described for Compound A of Example 234) in CH₂Cl₂ (3 ml) was added to a cooled solution of methyl triflate (2 mL, 17.6 mmol) in CH₂Cl₂ (10 mL) at -78° C over 30 min. The solution was slowly warmed to 0°C in 4 hrs. PBS Buffer (10 mL) was added and stirred for 20 min. The organic phase was separated. The aqueous layer was extracted with CH₂Cl₂ (2x10 mL). The combined organic layers were dried over Na₂SO₄ and evaporated to give an oil which was purified by RP preparative HPLC (gradient of aqueous methanol with 0.1% TFA) and converted to the HCl salt to afford Example 402 as a yellow solid. (60 mg, 289%)

MS (M+H)⁺ 498

Example 403



2,3,4,5-Tetrahydro-1-[(1-methyl-1H-imidazol-5-yl)-methyl]-4-(methylsulfonyl)-7-phenyl-3-(pyridin-3-yl-methyl)-1H-1,4-benzodiazepine, hydrochloride (1:1.5), trifluoroacetate (1:0.75) salt.

1-Methyl-5-formylimidazole (0.060 g, 0.54 mmol) was added to a solution of 2,3,4,5-tetrahydro-4-(methylsulfonyl)-7-phenyl-3-(pyridin-3-yl-methyl)-1H-1,4-benzodiazepine (0.11 g, 0.27 mmol, prepared as described in Example 328) with 3A molecular sieves (50 mg) in 1/1 DCE: acetic acid (1.8 ml) and the mixture was stirred at 70°C for 1h. Sodium

triacetoxyborohydrid (0.057 g, 0.27 mmol) was added and the mixture was stirred at 70°C for 30 minutes. 1-Methyl-5-formylimidazole (0.060 g, 0.54 mmol) was added to the mixture and it was stirred at 70°C for 1h. Sodium triacetoxyborohydride (0.057 g, 0.27 mmol) was added and the mixture was stirred at 70°C for 30 minutes. The latter procedure was repeated. The mixture was cooled to room temperature, diluted with methylene chloride (10 ml), filtered and the filtrate concentrated under vacuum. The residue was diluted with 1N NaOH (10 ml) and was stirred at room temperature for 10 minutes. The solution was extracted with CH₂Cl₂ (3X50 ml), the combined organic extracts were dried (Na₂SO₄), filtered and concentrated under vacuum. The residue was purified by preparative HPLC (gradient of aq MeOH with 0.1% TFA) and the appropriate fractions were isolated and concentrated under vacuum. The residue was evaporated from CH₃CN (5 ml) and 1N HCl (1 ml) 3 times. The residue was dissolved in CH₃CN (1 ml) and 1N HCl (2 ml) and lyophilized to afford Example 403 (0.025 g, 19%) as a white solid.

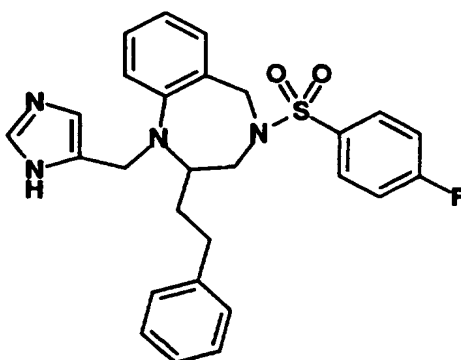
MS: (M+H)⁺ 488

Analysis calculated for C₂₇H₂₉N₅O₂S . 1.5 HCl . 2.02 H₂O . 0.75 TFA.

Calc'd: C, 51.54; H, 5.36; N, 10.54.

Found: C, 51.27; H, 5.72; N, 10.95.

Example 404



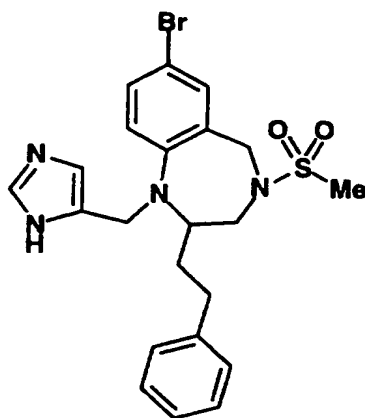
25 **4-[4-(Fluorophenyl)sulfonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-2-(2-phenylethyl)-1H-1,4-benzodiazepine, monohydrochloride.**

Example 404 was prepared as a solid in 41% yield from Compound A of Example 364 and 4-fluorobenzenesulfonyl chloride as described for Compound B of Example 364.

MS: (M+H)⁺ 491

5

Example 405



7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-yl-methyl)-4-(methylsulfonyl)-2-(2-phenylethyl)-1H-1,4-benzodiazepine, monohydrochloride.

A. 2,3,4,5-Tetrahydro-2-(2-phenylethyl)-1H-1,4-benzodiazepine

To a stirred solution of Compound A of Example 363 (140 mg, 0.52 mmol) in anhydrous THF at rt was added LAH (110 mg). The resultant suspension was stirred at rt for 18h, quenched by addition of ethyl acetate followed by 0.5 mL of concentrated NH₄OH solution and filtered. The filtrate was concentrated in vacuo to give Compound A as an oil (110 mg, 84%).

20

B. 2,3,4,5-Tetrahydro-4-(methylsulfonyl)-2-(2-phenylethyl)-1H-1,4-benzodiazepine

Compound B was prepared as an oil in 61% yield from Compound A as described for Compound C of Example 224.

25

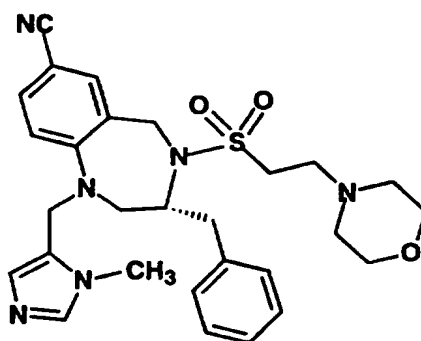
C. 7-Bromo-2,3,4,5-tetrahydro-4-(methylsulfonyl)-2-(2-phenylethyl)-1H-1,4-benzodiazepine

To a stirred solution of Compound C (80 mg, 0.24 mmol) in CHCl_3 was added tetrabutylammonium perbromide (120 mg, 0.24 mmol) in one portion. The mixture was stirred at room temperature for 30 min and evaporated. The residue was partitioned between water and 50% ethyl acetate and hexanes. The organic layer was separated, washed with water, sat'd NH_4Cl solution, dried, and concentrated to give Compound C as an oil (100 mg, 100%).

D. 7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-yl-methyl)-4-(methylsulfonyl)-2-(2-phenylethyl)-1H-1,4-benzodiazepine, monohydrochloride

Compound D was prepared as a solid in 92% yield from Compound C as described for Compound D of Example 224.
MS: $(\text{M}+\text{H})^+$ 489

Example 406



(R)-7-Cyano-2,3,4,5-tetrahydro-1-(1-methyl-1H-imidazol-5-ylmethyl)-4-[[2-(1-morpholinyl)ethyl]sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.

A. (R)-7-Cyano-2,3,4,5-tetrahydro-4-[ethenylsulfonyl]-3-(phenyl-methyl)-1H-1,4-benzodiazepine

2-Chloroethanesulfonyl chloride (1.85 g, 11.4 mmol) was added to a solution of Compound C of Example 248 (1.0 g, 3.79 mmol) and DIEA (2.6 mL, 15.16 mmol) in dichloromethane (16 mL) at 0°C under argon. After stirring for 16 hr, the reaction was diluted with chloroform (20mL) and

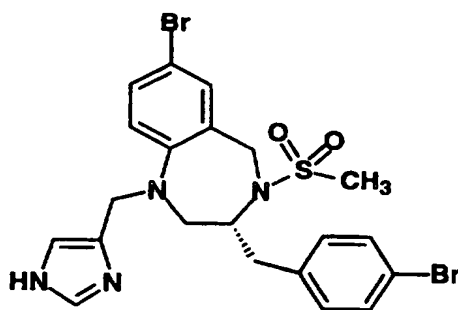
NaHCO₃ (5 mL). The layers were separated, the aqueous layer was extracted with chloroform (2 x 50 mL). The combined organic extracts were washed with NaHCO₃ (2 x 20 mL) and brine (2 x 50 mL), dried over MgSO₄, filtered and concentrated, to afford Compound A (1.55 g, 116.5 %).

B. (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1-methyl-1H-imidazol-5-ylmethyl)-4-[[2-(1-morpholinyl)ethyl]sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride

Compound B was prepared as a light yellow solid in 12% overall yield by the following sequence: Compound B of Example 353, with chromatography with 1:1 ethyl acetate:hexanes; Compound C of Example 353, with reaction at room temperature, stirring for 2 days and purification by RP preparative HPLC (gradient of aqueous methanol with 0.1% TFA).

MS: (M+H)⁺ 535

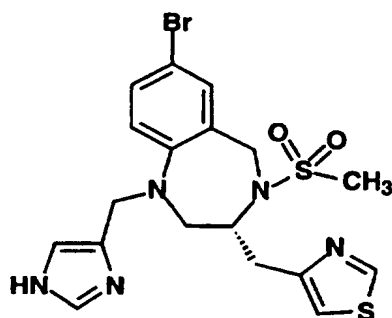
Example 407



(R)-7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(4-bromophenylmethyl)-1H-1,4-benzodiazepine, hydrochloride.

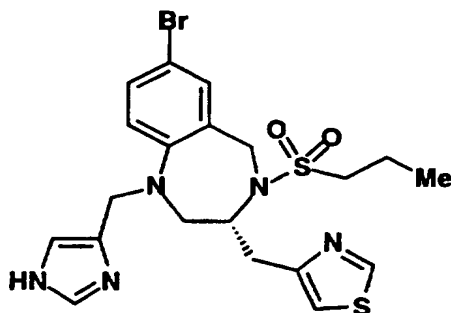
Example 407 was prepared from D-4-bromophenylalanine as described for Example 224; the crude product was purified by RP preparative HPLC (gradient of aqueous methanol with 0.1% TFA). Fractions containing the desired product were combined, neutralized with saturated Na₂CO₃ aqueous solution and extracted with CH₂Cl₂. The combined extracts were dried (Na₂SO₄) and evaporated under reduced pressure. The residue was dissolved in ethyl acetate (10 mL) and 1N HCl solution in ether (10 mL) was added. The solvent was removed in vacuo to give Example 407 as a yellow solid.

MS (M+H)⁺ 555

Exempl 408

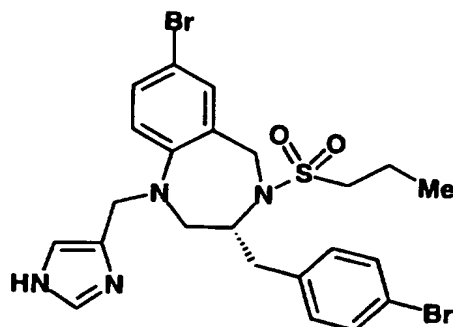
- 5 **(R)-7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methyl-sulfonyl)-3-(thiazol-4-ylmethyl)-1H-1,4-benzodiazepine, hydrochloride.**

Example 408 was prepared as a yellow solid from D-(thiazol-4-yl)alanine methyl ester as described for Example 407.
 10 MS (M+H)⁺ 484

Example 409

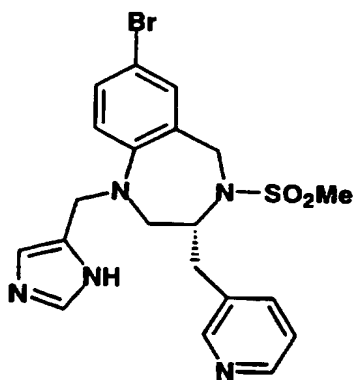
- 15 **(R)-7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(propyl-sulfonyl)-3-(thiazol-4-ylmethyl)-1H-1,4-benzodiazepine, hydrochloride.**

20 Example 409 was prepared as described for Example 408, except that propanesulfonyl chloride was used in place of methanesulfonyl chloride.
 MS (M+H)⁺ 510.

Example 410

- 5 **(R)-7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(propylsulfonyl)-3-(4-bromophenylmethyl)-1H-1,4-benzodiazepine, hydrochloride.**

Example 410 was prepared as described for Example 407, except
that propanesulfonyl chloride was used in place of methanesulfonyl chloride.
10 MS (M+H)⁺ 583

Example 411

- 15 **(R)-7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(pyridin-3-ylmethyl)-4-(methylsulfonyl)-1H-1,4-benzodiazepine, trihydrochloride.**

Example 411 was prepared as a pale yellow solid in 16% yield
from Compound A of Example 350 by the following sequence: Compound C
of Example 350, with the addition done at 0°C and chromatography with
ethyl acetate; Compound D of Example 350, with heating at 60°C.
20 (M+H)⁺ 476.

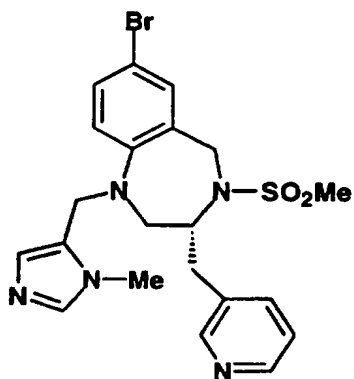
Analysis calculated for $C_{20}H_{22}N_5BrO_2S \cdot 3.00HCl \cdot 0.17H_2O$.

Calc'd: C, 40.80; H, 4.34; N, 11.89.

Found: C, 40.79; H, 4.36; N, 11.79.

5

Example 412



10 **(R)-7-Bromo-2,3,4,5-tetrahydro-1-(1H-1-methyl-imidazol-5-ylmethyl)-3-(pyridin-3-ylmethyl)-4-(methanesulfonyl)-1H-1,4-benzodiazepine, dihydrochloride.**

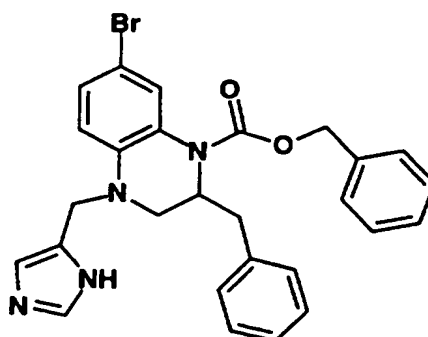
Example 412 was prepared as a pale yellow solid in 31% yield from (R)-7-bromo-2,3,4,5-tetrahydro-3-(pyridin-3-ylmethyl)-4-(methanesulfonyl)-1H-1,4-benzodiazepine (prepared as described in Example 411) and 1-methyl-5-formylimidazole as described for Compound D of Example 350, with heating at 60°C.

15 (M+H)⁺ 490.

Analysis calculated for $C_{21}H_{24}N_5BrO_2S \cdot 2.25HCl \cdot 1.38H_2O$.

Calc'd: C, 42.23; H, 4.90; N, 11.72.

20 Found: C, 42.23; H, 4.90; N, 11.66.

Exempl 413

5 **1,2,3,4-Tetrahydro-7-bromo-4-[(1H-imidazol-4-yl)methyl]-2-phenyl-methyl-1-(phenylmethyloxycarbonyl)quinoxaline, hydrochloride.**

A. N-(2-Nitrophenyl)-phenylalanine

10 To a suspension of DL-phenylalanine (490 mg, 3 mmol) in water at rt was added sodium bicarbonate (0.84 g, 10 mmol) and 2-fluoronitrobenzene (0.63 mL, 6 mmol). The mixture was heated to 80°C. After 16 hr, ethanol (95%, 3 mL) was added. After 6 hr, the mixture was partially concentrated to remove ethanol and the resulting solution was washed with ethyl acetate and chloroform (10 mL each). The aqueous layer
15 was acidified to pH 1 and extracted with chloroform (2 x 10 mL). The chloroform extracts were combined, dried (MgSO₄), and concentrated in vacuo to afford Compound A as a solid (0.81g, 94%). MS (M+H)⁺ 287

B. N-(2-Nitrophenyl)-phenylalanine, methyl ester

20 To a solution of Compound A (780 mg, 2.7 mmol) in MeOH (15 mL) at rt was added HCl in dioxane (3 mL, 4M). After 18 hr, the mixture was concentrated. The residue was dissolved in chloroform (15 mL) and washed with saturated NaHCO₃ (10 mL) and brine (15 mL). The organic layer was dried (MgSO₄) and concentrated in vacuo. The yellow oil was
25 chromatographed (silica, flash, 20% EtOAc/hexanes) to afford Compound B (740 mg, 91%) as a yellow solid. MS (M+H)⁺ 301

C. 1,2,3,4-Tetrahydro-3-oxo-2-phenylmethyl-quinoxaline

30 To a solution of Compound B (720 mg, 2.34 mmol) in ethyl acetate (5 mL) at rt was added 20% Pd(OH)₂/C (40 mg). The flask was filled with

hydrogen gas via a balloon. After 5 hr, the mixture was filtered through celite, and the filtrate was concentrated in vacuo. The colorless solid was chromatographed (silica, flash, 30% EtOAc/hexanes) to afford Compound C (550 mg, 98%) as a solid. MS (M+H)+ 239.

5

D. 1,2,3,4-Tetrahydro-3-oxo-2-phenylmethyl-1-(phenylmethoxy-carbonyl)quinoxaline

To a solution of Compound C (525 mg, 2.2 mmol) in dichloromethane (6 mL) at 0°C were added DIEA (0.52 mL, 3 mmol) and benzylchloroformate. The mixture was allowed to warm to rt over 3 hr. DMAP (10 mg) and pyridine (1 mL) were added and the mixture was stirred overnight (16 hr). The mixture was concentrated in vacuo and the residue was partitioned between ethyl acetate (20 mL) and 1N HCl (15 mL). The organic layer was separated, washed with 1N HCl (15 mL), dried (MgSO₄), and concentrated in vacuo. The residue was chromatographed (silica, flash, 10% EtOAc/chloroform) to afford Compound D as a solid (440 mg, 54%). MS (M+H)+ 373.1.

E. 1,2,3,4-Tetrahydro-2-phenylmethyl-1-(phenylmethoxy-carbonyl)quinoxaline

A mixture of Compound D (380 mg, 1.02 mmol) and borane in THF (1 M, 3 mL) was stirred at rt under argon. After 24 hr, MeOH (10 mL) was added carefully followed by 1N HCl (1M in ether, 5 mL). After 1 hr, the mixture was concentrated in vacuo. The above procedure was repeated once more to afford a white solid which was then treated with chloroform and 10% ammonium hydroxide (20 mL each) and stirred vigorously. After 1 hr, the organic layer was separated, dried (MgSO₄), and concentrated in vacuo to afford Compound E as a solid (366 mg, 100%). MS (M+H)+ 359.1.

F. 1,2,3,4-Tetrahydro-7-bromo-2-phenylmethyl-1-(phenylmethyl-oxycarbonyl)quinoxaline

To a stirred solution of Compound E (340 mg, 0.95 mmol) in chloroform (3 mL) at rt was added a solution of tetrabutylammonium tribromide (457 mg, 0.95 mmol) in chloroform (2 mL) over 2 min. After 10 min, an aqueous solution of sodium bisulfite (10 mL) was added and the mixture was extracted with chloroform (10 mL). The organic layer was separated, dried (MgSO₄), and concentrated in vacuo. The residue was

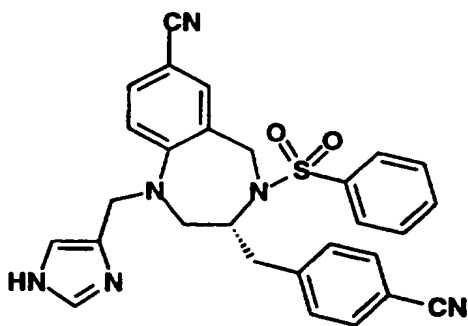
chromatographed (silica, flash, 15% EtOAc/hexanes) to afford Compound F (355 mg, 86%) as a thick oil. MS (M+H)⁺ 437, 439.

G. 1,2,3,4-Tetrahydro-7-bromo-4-[(1H-imidazol-4-yl)methyl]-2-phenylmethyl-1-(phenylmethyloxycarbonyl)quinoxaline, hydrochloride

To a solution of Compound F (345 mg, 0.79 mmol) in dichloromethane (3 mL) at rt were added 4-formylimidazole (0.3 g, 3.1 mmol), acetic acid (1 mL), 3A sieves and sodium triacetoxymethylborohydride (212 mg, 1 mmol). After 5hr, sodium borohydride (212 mg, 1 mmol) was added. After 15hr, the mixture was filtered and the filtrate concentrated in vacuo. The residue was dissolved in chloroform (15 mL) and stirred vigorously with aqueous ammonia (15 mL). After 1 hr, the organic layer was separated, dried (MgSO₄) and concentrated in vacuo. Chromatography (silica, flash, 10% i-PrOH in chloroform) afforded the free base (280 mg, 69%). 1N HCl in ether (2 mL) was added to this solid (25 mg) and the mixture was dried in vacuo to afford Compound G (28 mg). MS (M+H)⁺ = 517, 519.

20

Example 414



(R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(phenylsulfonyl)-3-(4-cyanophenylmethyl)-1H-1,4-benzodiazepine, hydrochloride.

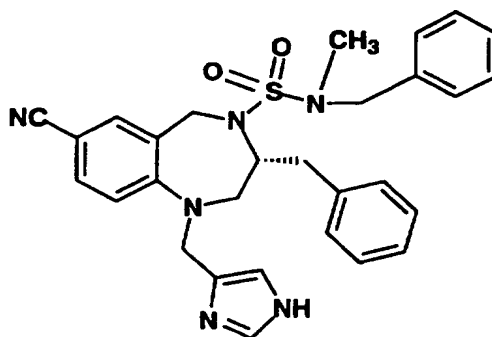
Example 414 was prepared as a solid in 12% yield from (R)-7-bromo-2,3,4,5-tetrahydro-3-(4-bromophenylmethyl)-1H-1,4-benzodiazepine (prepared as described in Example 407) by the following sequence:

Compound C of Example 248; Compound C of Example 224, using benzenesulfonyl chloride; Compound D of Example 224, with purification by reverse phase preparative HPLC (gradient of aq methanol with 0.1% TFA). MS (M+H)⁺ 509,

- 5 ¹³C NMR (CD₃OD, 100 MHz) 39.60, 47.69, 50.29, 55.65, 60.46, 102.42, 111.55, 116.13, 118.47, 119.87, 125.00, 128.22, 129.73, 132.14, 133.34, 133.48, 133.62, 135.32, 136.22, 141.24, 144.60, 152.53 ppm.

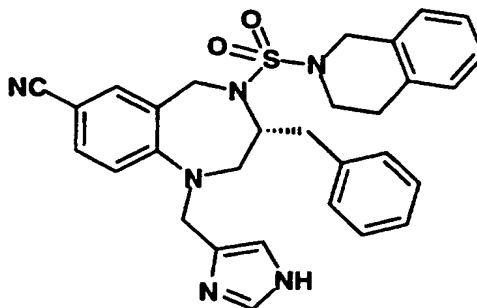
Example 415

10



- 15 **(R)-7-Cyano-4-[(N-methyl-N-phenylmethyl)aminosulfonyl]-1-[(1H-imidazol-4-yl)methyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.**

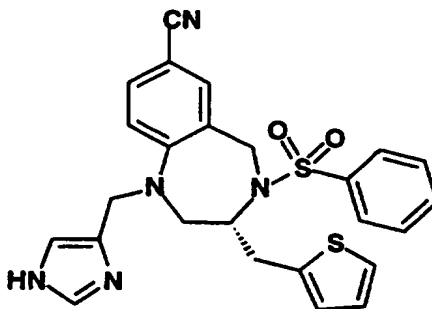
Example 415 was prepared as a fluffy solid in 8% yield from N-methyl-N-phenylmethyl-sulfamoyl chloride and Compound C of Example 248 by the following sequence: Compound A of Example 355, with reaction
20 at 0°C to room temperature and chromatography with 20% ethyl acetate/hexanes; Compound C of Example 353, with reaction at reflux in the presence of 3A sieves.
MS: [M+H]⁺ = 527.

Example 416

- 5 **(R)-7-Cyano-4-[N-(tetrahydroisoquinoliny)sulfonyl]-1-[(1H-imidazol-4-yl)methyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.**

Example 416 was prepared as a white solid in 11% yield from
 10 tetrahydroisoquinolinyisulfamoyl chloride and Compound C of Example 248 as described for Example 415.

MS: $[M+H]^+ = 539$.

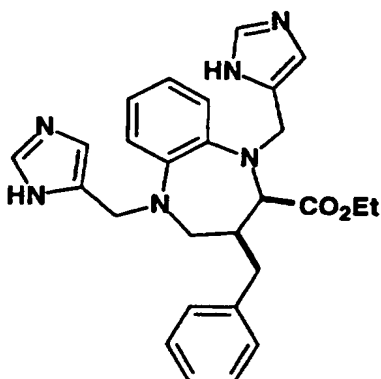
Example 417

- 15 **(R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(phenylsulfonyl)-3-(2-thienylmethyl)-1H-1,4-benzodiazepine, hydrochloride.**

20

Example 417 was prepared as a yellow solid from 2-(thienyl)alanine and bromoisatoic anhydride as described for Example 407, using benz nesulfonyl chloride in place of methanesulfonyl chlorid .

MS $(M+H)^+ 490$.

Example 418

5 **cis-2,3,4,5-Tetrahydro-1,5-bis(1H-imidazol-4-ylmethyl)-3-(phenyl-methyl)-1H-1,5-benzodiazepine-2-carboxylic acid ethyl ester, trifluoroacetate (1:2).**

A. **2-Oxo-3-phenylmethyl-but-3-enoic acid, ethyl ester**

10 A solution of ethyl-2-oxo-4-phenylbutyrate (31.8 mmol, 6.0 mL), N,N,N',N'-tetramethyldiaminomethane (6.6 mL, 54 mmol) and acetic anhydride (10 mL, 106 mmol) in DMF (100 mL) was stirred at room temperature for 16 hours and evaporated. The residue was chromatographed (flash silica, 20% EtOAc/Hexanes) to afford Compound A
15 as a clear oil (6.46 g, 93%). MS (M+NH₄)⁺ 236.

B. **2,3-Dihydro-3-(phenylmethyl)-1H-1,5-benzodiazepine-2-carboxylic acid ethyl ester**

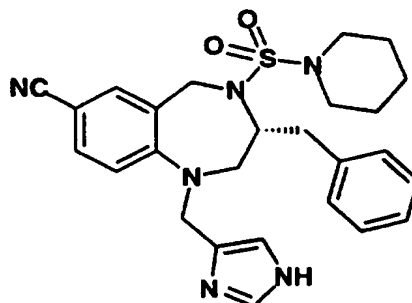
20 A mixture of Compound A (6.46 g, 29.6 mmol), phenylenediamine (3.5 g, 32.6 mmol) and hydroquinone (300 mg, 2.72 mmol) in toluene (250 mL) was heated to reflux under Dean-Stark conditions for 6 hours. The mixture was concentrated and the residue was purified by flash chromatography (20% EtOAc/Hexanes) affording compound B as viscous
25 yellow oil (3.3g, 36%). MS (M+H)⁺ 309.

C. **cis-2,3,4,5-Tetrahydro-1,5-bis(1H-imidazol-4-ylmethyl)-3-(phenyl-methyl)-1H-1,5-benzodiazepine-2-carboxylic acid ethyl ester, trifluoroacetate (1:2)**

Compound B (165 mg, 0.76 mmol) was dissolved in 2 mL AcOH and 2 mL CH₂Cl₂ and treated with 4-formylimidazole (183 mg, 1.9 mmol) and NaBH(OAc)₃ (645 mg, 3.0 mmol). The mixture was stirred at room temperature for 16 hours, concentrated and partitioned between saturated NaHCO₃ (50 mL) and 10% isopropanol-CH₂Cl₂. The organic phase was washed with saturated NaHCO₃ (50 mL), dried over Na₂SO₄, dissolved in MeOH (2 mL) and purified by reverse phase preparative HPLC (gradient of aqueous methanol with 0.1% TFA) to afford a yellow oil (120 mg, 23%), which was lyophilized from water to yield Compound C as an off-white fluffy solid.

MS (M+H)⁺ 471.

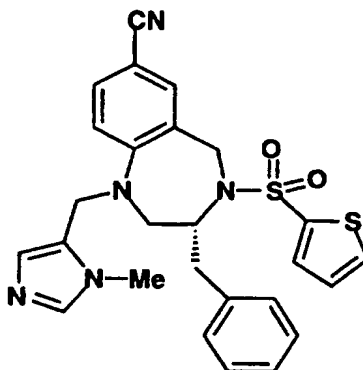
Example 419



(R)-7-Cyano-4-[(N-piperidiny)sulfonyl]-1-[(1H-imidazol-4-yl)methyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.

Example 419 was prepared as a fluffy white solid in 26% yield from N-piperidiny)sulfamoyl chloride and Compound C of Example 248 as described for Example 415, with the final chromatography using 5% methanol/chloroform.

MS (M+H)⁺ = 491.

Example 420

5 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-1-methyl-imidazol-5-ylmethyl)-3-(phenylmethyl)-4-(2-thienylsulfonyl)-1H-1,4-benzodiazepine, hydrochloride.

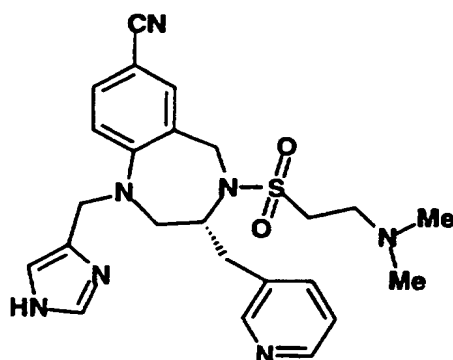
A mixture of Compound A of Example 284 (150 mg, 0.366 mmol),
 10 1-methyl-5-formylimidazole (121 mg, 1.10 mmol) and 200 mg of 3A
 molecular sieves in 2 mL of 3:1 DCE/AcOH was heated at 60°C. At 1 hr, 4
 hr, 7 hr and 10 hr, aliquots of sodium triacetoxyborohydride (116 mg, 0.549
 mmol) were added. At 3 hr, 6 hr and 9 hr, aliquots of aldehyde (91 mg, 0.946
 mmol) were added. Acetic acid (1 mL) was also added at 9 hr. Following
 15 the last addition of hydride, the mixture was stirred at 60°C for 2 hr diluted
 with 5 mL of methanol, filtered, and concentrated in vacuo. The residue was
 diluted with 100 mL of EtOAc and washed with 1N NaOH (3 x 50 mL), and
 brine. The organic layer was dried over Na₂SO₄, filtered and concentrated
 in vacuo. The residue was purified by reverse phase preparative HPLC
 20 (gradient of aqueous methanol with 0.1% TFA) and the appropriate fractions
 were concentrated. The residue was dissolved in 1M HCl (3 x 5 mL) and
 concentrated in vacuo. The residue was dissolved in minimal acetonitrile,
 diluted with water and freeze-dried to provide 60 mg (29%) of Example 420
 as a white solid.

25 (M+H)⁺ 504.

Analysis calculated for C₂₆H₂₅N₅O₂S₂ • 1.50 HCl • 0.66 H₂O.

Calc'd: C, 54.77; H, 4.92; N, 12.28.

Found: C, 54.77; H, 4.92; N, 12.25.

Example 421

5

(R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(pyridin-3-ylmethyl)-4-[[2-(dimethylamino)ethyl]sulfonyl]-1H-1,4-benzodiazepine, trihydrochloride.

10 **A. (R)-7-Cyano-2,3,4,5-tetrahydro-3-(pyridin-3-ylmethyl)-4-[[2-(dimethylamino)ethyl]sulfonyl]-1H-1,4-benzodiazepine**

2-Chloroethane sulfonyl chloride (0.79 ml, 7.6 mmol) was added to a solution of Compound B of Example 350 (1.0 g, 3.8 mmol) and DIEA (0.66 ml, 3.8 mmol) in CH₂Cl₂ at -78°C. The mixture was stirred at -78°C for 15 minutes. DIEA (0.66 ml, 3.8 mmol) was added and the mixture was stirred at -78°C for 1h. DIEA (2.6 ml, 15.2 mmol) was again added to the reaction mixture at -78°C. The mixture was allowed to warm to room temperature and stirring was continued for 16h. The solution was concentrated under vacuum. The residue was dissolved in 3/1 THF/CH₂Cl₂ (4 ml). The mixture was saturated with dimethylamine, condensed using a dry-ice cold finger at room temperature. The mixture was stirred at room temperature for 2h. The resulting solution was diluted with 10% NaHCO₃ (100 ml) and the solution was extracted with 9/1 CH₂Cl₂/iPrOH (3X150 ml). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated under vacuum to afford Compound A (1.5g, 100%). MS: (M+H)⁺ 400

25

B. (R)-7-Cyan -2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(pyridin-3-ylmethyl)-4-[[2-(dimethylaminomethyl)sulfonyl]-1H-1,4-benzodiazepin-5-yl]trihydrochloride

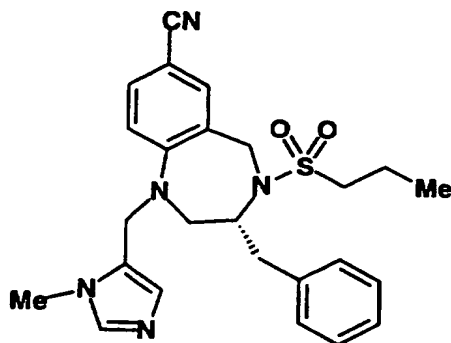
5 4-Formylimidazole (0.14 g, 1.5 mmol) was added to a solution of 1
(0.30 g, 0.75 mmol) and 3A molecular sieves in 1/1 DCE: acetic acid (5 ml)
and the mixture was stirred at 70°C for 0.5h. Sodium triacetoxyborohydride
(0.32 g, 1.5 mmol) was added and the mixture was stirred at 70°C for 15
10 minutes. 4-Formylimidazole (0.14 g, 1.5 mmol) was added and the mixture
was stirred at 70°C for 0.5h. Sodium triacetoxyborohydride (0.32 g, 1.5
mmol) was added and the mixture was stirred at 70°C for 15 minutes. The
latter two steps were repeated four times. The mixture was cooled to room
temperature, diluted with methylene chloride (30 ml), filtered and the filtrate
concentrated under vacuum. The residue was diluted with 25% NH₄OH (50
15 ml) and the solution was extracted with 9/1 CH₂Cl₂/iPrOH (4X50 ml). The
combined organic extracts were dried (Na₂SO₄), filtered and concentrated
under vacuum. The residue was purified by reverse phase preparative
HPLC (gradient of aq MeOH with 0.1% TFA) and the appropriate fractions
were isolated and concentrated under vacuum. The residue was
20 evaporated from 1/1 CH₃OH/1N HCl (2 ml) 5X. The residue was dissolved in
CH₃CN (2 ml) and 1N HCl (4 ml) and lyophilized to afford Compound B
(0.071 g, 16 %) as a solid.

MS: (M+H)⁺ 480

Analysis calculated for C₂₄H₂₉N₇O₂S • 3.3 HCl • 0.74 H₂O.

25 Calc'd: C, 47.01; H, 5.55; N, 15.99; S, 5.23; Cl, 19.08.

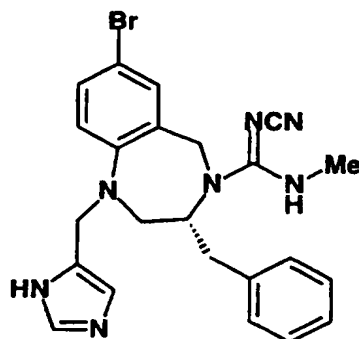
Found: C, 47.00; H, 5.43; N, 15.53; S, 5.00; Cl, 18.98.

Example 422

5 **(R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-1-methyl-imidazol-5-ylmethyl)-3-(phenylmethyl)-4-(propylsulfonyl)-1H-1,4-benzodiazepine, hydrochloride.**

A solution of 320 mg (0.87 mmol) of Compound A of Example 317 in 5 mL of dichloroethane and 500 mL of glacial acetic acid was treated with
10 478 mg (4.34 mmol) of 1-methyl-imidazole-5-carboxaldehyde and 3A sieves. The mixture was heated to 60°C, stirred for 5 hrs and treated with 763 mg (3.60 mmol) of sodium triacetoxyborohydride. The mixture was allowed to cool to rt, stirred for 18 hrs
and filtered. The filtrate was concentrated in vacuo. The residue was
15 partitioned between 150 mL of 1N sodium hydroxide and 150 mL of ethyl acetate. The organic layer was washed with brine, dried (Na₂SO₄), filtered and concentrated in vacuo. The brown oil was purified by reverse phase preparative HPLC (gradient of aq methanol with 0.1% TFA). The resulting white foam was evaporated 3X from methanolic hydrogen chloride. The
20 white foam was dissolved in water and lyophilized to afford Example 422 (59 mg, 15%) as a white lyophilate.

MS: (M+H)⁺ = 464⁺

Example 423

5 **N-(Cyano)-N'-methyl-1,2,3,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4H-1,4-benzodiazepine-4-imidamide, hydrochloride.**

A. N-(Cyano)-O-phenyl-1,2,3,5-tetrahydro-7-phenyl-4H-1,4-benzodiazepine-4-imidate

10 A solution of 500 mg (1.58 mmol) of Compound B of Example 224 in 20 mL of DMF was treated, under argon, with 390 mg (1.64 mmol) of diphenyl cyanocarbonimide followed by 275 μ L (1.58 mmol) of DIEA and 97 mg (0.79 mmol) of DMAP. The mixture was stirred at rt for 15 min, at 80°C for 3.5 hrs and at rt for 80 hrs. The mixture was partitioned between 250 mL
15 of ethyl acetate and 250 mL of 1N sodium hydroxide. The aqueous layer was extracted 3x with 100 mL of ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The oil was purified by flash chromatography (silica, 40% ethyl acetate/hexane) to give 456 mg (63%) of Compound A as a white solid.

20

B. N-(Cyano)-N'-methyl-1,2,3,5-tetrahydro-7-phenyl-4H-1,4-benzodiazepine-4-imidamide

A solution of 180 mg (0.39 mmol) of Compound A in 1mL of DMF was treated with 242 μ L (1.94 mmol) of a solution of 33% methylamine in
25 ethanol. The mixture was stirred at rt for 1hr and concentrated. The residue was dissolved in 100 mL of ethyl acetate, washed with brine, dried (Na_2SO_4) and concentrated in vacuo to give 125 mg (87%) of Compound B as a white solid. MS ($\text{M}+\text{H}$)⁺ = 400.

C. N-(Cyano)-N'-methyl-1,2,3,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4H-1,4-benzodiazepin-4-imidamide, hydrochloride

A solution of 115 mg (0.29 mmol) of Compound B in 2.5 mL of dichloroethane and 2.5 mL of glacial acetic acid was treated with 69 mg (0.71 mmol) of 4-imidazole-carboxaldehyde, 3A sieves and stirred at rt for 18hrs. The mixture was treated with 122 mg (0.58 mmol) of sodium triacetoxyborohydride in one portion and stirred at rt for 30min and filtered. The filtrate was partitioned between 100 mL of ethyl acetate and 100 mL of 1N sodium hydroxide. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The oil was purified by reverse phase preparative HPLC (gradient of aq methanol with 0.1% TFA). The yellow foam was evaporated 3X from methanolic hydrogen chloride. The foam was dissolved in water and lyophilized to afford 30 mg (22%) of Compound C as a yellow lyophilate.

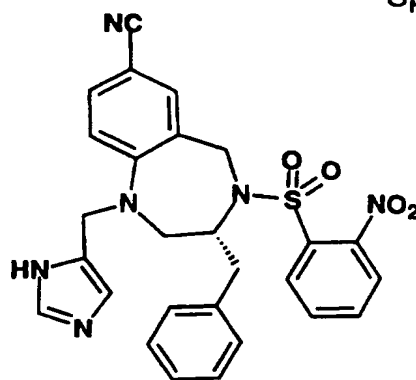
MS: $(\text{M}+\text{H})^+ = 480$.

Example 424-430

Examples 424-430 were prepared from Compound C of Example 248 and the appropriate sulfonyl chloride as described by the following sequence: Compound A of Example 299; Compound B of Example 317. Satisfactory C, H and N analyses were obtained for Examples 424-430.

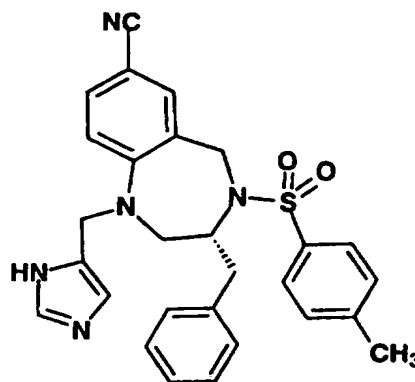
Example

424 (R)-7-Cyano-4-[(2-nitrophenyl)-sulfonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenyl-methyl)-1H-1,4-benzodiazepine, hydrochloride.



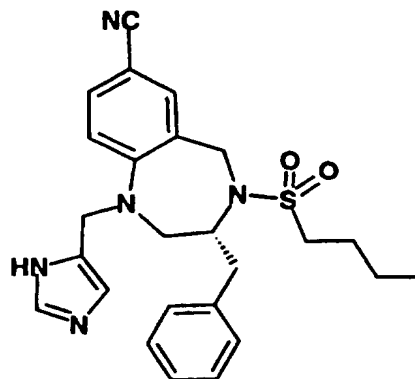
Mass
Spectrum
m/z
529
(M+H)

- 425 (R)-7-Cyano-4-[(4-methylphenyl)sulfonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, hydrochloride.



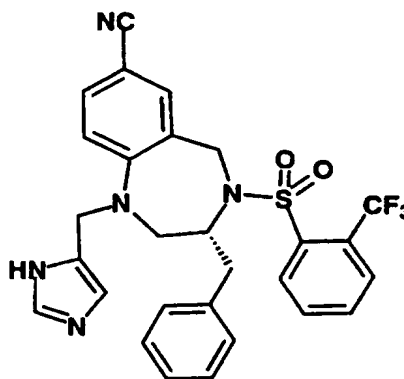
m/z
498
(M+H)

- 426 (R)-7-Cyano-4-(butylsulfonyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, hydrochloride.



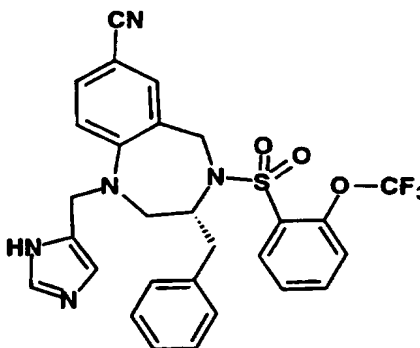
m/z
464
(M+H)

- 427 (R)-7-Cyano-4-[(2-trifluoromethylphenyl)sulfonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, hydrochloride.



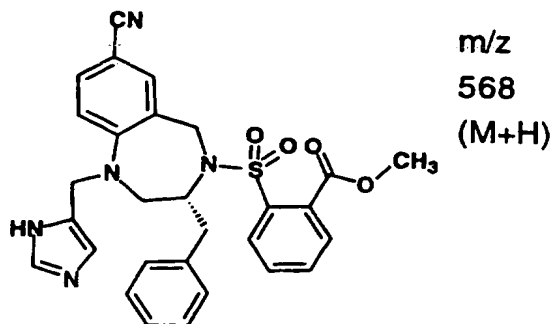
m/z
552
(M+H)

- 428 (R)-7-Cyano-4-[(2-trifluoromethoxyphenyl)sulfonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, hydrochloride.

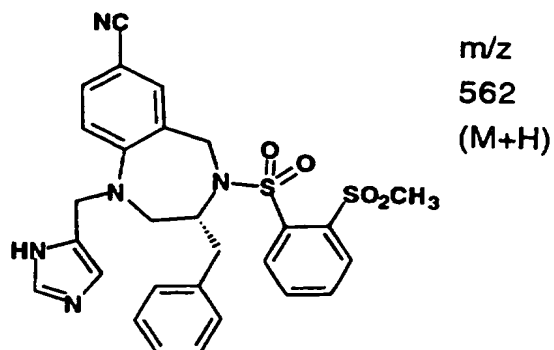


m/z
568
(M+H)

- 429 (R)-7-Cyano-4-[(2-methoxycarbonylphenyl)sulfonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, hydrochloride.



- 430 (R)-7-Cyano-4-[(2-methylsulfonylphenyl)sulfonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, hydrochloride.



Example 431

The following examples were prepared using the methods described herein as well as by methods known to those skilled in the art.

5

(R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(((4-methylsulfonyl)-phenyl)-sulfonyl)-1H-1,4-benzodiazepine	m/z 562 (M+H)
(R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(((4-trifluoromethyl)-phenyl)-sulfonyl)-1H-1,4-benzodiazepine	m/z 552 (M+H)
(R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-((3-methoxypropyl)-sulfonyl)-1H-1,4-benzodiazepine	m/z 480 (M+H)
(R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-((3,4-dimethoxyphenyl)-sulfonyl)-1H-1,4-benzodiazepine	m/z 544 (M+H)
(R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-((4-fluorophenyl)methyl)-4-(phenylsulfonyl)-1H-1,4-benzodiazepine	m/z 502 (M+H)
(R)-7-Cyano-4-[(N-cyclopropylmethyl-N-propyl)-aminosulfonyl]-1-[(1H-imidazol-4-yl)methyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine	m/z 519 (M+H)
(R)-7-Cyano-4-[(N,N-(dibutylamino))-sulfonyl]-1-[(1H-imidazol-4-yl)methyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine	m/z 535 (M+H)
(R)-7-Chloro-4-(methanesulfonyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-pyrido[3,4-e]-1,4-diazepine	m/z 432 (M+H)
1,2,3,4-Tetrahydro-7-bromo-4-[(1H-imidazol-4-yl)methyl]-2-phenylmethyl-1-(methylsulfonyl)quinoxaline	m/z 460 (M+H)
(R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-((imidazol-4-yl)methylsulfonyl)-1H-1,4-benzodiazepine	m/z 424 (M+H)

Following the above procedures, the following compounds may be made:

- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-((2-thienyl)methyl)-4-(propylsulfonyl)-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-((2-thienyl)methyl)-4-((2-thienyl)-sulfonyl)-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-((3-methylthiopropyl)-sulfonyl)-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(((3-methylthio)-propyl)-sulfonyl)-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(((3-methylsulfonyl)-propyl)-sulfonyl)-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-((2-methylpropyl)-sulfonyl)-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(cyclopentylsulfonyl)-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-((4,4,4-trifluorobutyl)-sulfonyl)-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-((phenylmethyl)-sulfonyl)-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-[[2-(5-(N-benzoyl)-aminomethyl)-thienyl]-sulfonyl]-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-[[2-(1-(3-chloro-5-methyl-pyridin-2-yl))-pyrrolyl]-sulfonyl]-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-((4-carboxyphenyl)-sulfonyl)-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(((3-methyl-1,2,4-oxadiazol-5-yl)-phenyl)-sulfonyl]-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-((2,5-dimethoxyphenyl)-sulfonyl)-1H-1,4-benzodiazepine
- (R)-7-Cyano-4-[(N-tetrahydroquinolinyl)sulfonyl]-1-[(1H-imidazol-4-yl)methyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine

- (R)-7-Cyano-4-[(N,N-bis-[1-(2-methylpropyl)amino]-sulfonyl)-1-[(1H-imidazol-4-yl)methyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine
- (R)-7-Cyano-4-[(N-methyl-N-phenyl)aminosulfonyl]-1-[(1H-imidazol-4-yl)methyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine
- 5 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(2-(2,6-dimethylphenyl)-ethyl)-4-(methylsulfonyl)-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1-(N-phthalimidoethyl)-imidazol-5-ylmethyl)-3-(phenylmethyl)-4-(methylsulfonyl)-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-[(2-(N,N-dimethylamino)-ethyl)-imidazol-5-ylmethyl]-3-(phenylmethyl)-4-(methylsulfonyl)-1H-1,4-benzodiazepine
- 10 (R)-7-Cyano-2,3,4,5-tetrahydro-1-[(2-aminoethyl)-imidazol-5-ylmethyl]-3-(phenylmethyl)-4-(methylsulfonyl)-1H-1,4-benzodiazepine
- (R)-7-Bromo-4-(methanesulfonyl)-2,3,4,5-tetrahydro-1-[(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-thieno[2,3-e]-1,4-diazepine
- 15 (R)-7-Bromo-4-(methanesulfonyl)-2,3,4,5-tetrahydro-1-[(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-thieno[3,2-e]-1,4-diazepine
- (R)-4-(methanesulfonyl)-2,3,4,5-tetrahydro-1-[(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-8-oxo-pyrimidino[4,5-e]-1,4-diazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-((4-(2-methoxyethoxy)-phenyl)methyl)-4-(phenylsulfonyl)-1H-1,4-benzodiazepine
- 20 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-((4-(2-(dimethylamino)-ethoxy)-phenyl)methyl)-4-(phenylsulfonyl)-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylsulfonyl)-3-(phenylmethyl)-4-(methylsulfonyl)-1H-1,4-benzodiazepine
- 25 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylsulfonyl)-3-(phenylmethyl)-4-(propylsulfonyl)-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylsulfonyl)-3-(phenylmethyl)-4-(phenylsulfonyl)-1H-1,4-benzodiazepine
- 30 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylsulfonyl)-3-(phenylmethyl)-4-(2-thienylsulfonyl)-1H-1,4-benzodiazepine
- 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(R)-[(R)-1-phenylethyl]-4-(methylsulfonyl)-1H-1,4-benzodiazepine
- 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(R)-[(R)-1-phenylethyl]-4-(propylsulfonyl)-1H-1,4-benzodiazepine
- 35 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(R)-[(R)-1-phenylethyl]-4-(phenylsulfonyl)-1H-1,4-benzodiazepine

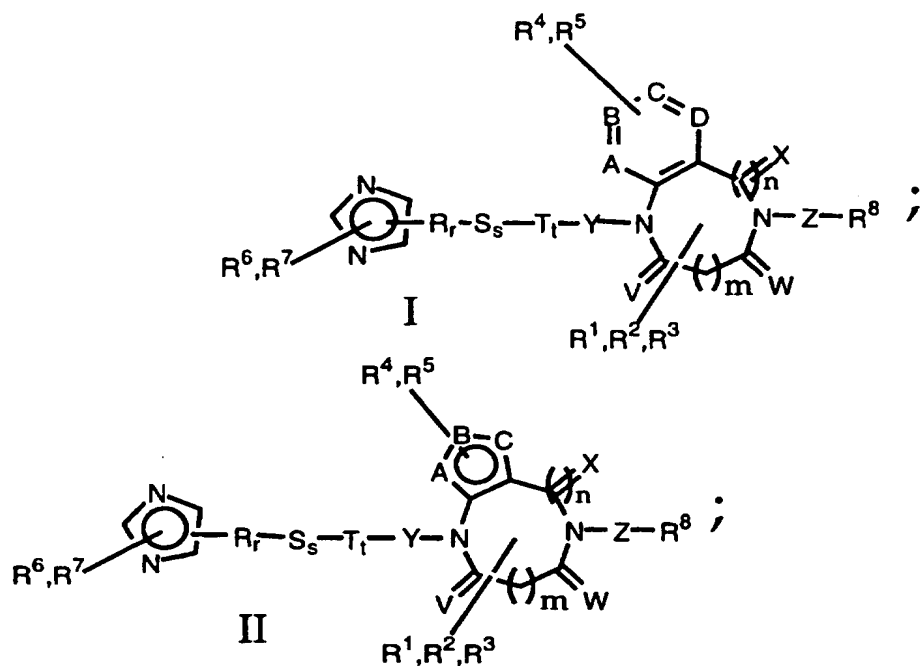
- 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(R)-[(R)-1-phenyl-ethyl]-4-((2-thienyl)-sulfonyl)-1H-1,4-benzodiazepine
- 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(S)-[(R)-1-phenyl-ethyl]-4-(methylsulfonyl)-1H-1,4-benzodiazepine
- 5 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(S)-[(R)-1-phenyl-ethyl]-4-(propylsulfonyl)-1H-1,4-benzodiazepine
- 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(S)-[(R)-1-phenyl-ethyl]-4-(phenylsulfonyl)-1H-1,4-benzodiazepine
- 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(S)-[(R)-1-phenyl-ethyl]-4-((2-thienyl)-sulfonyl)-1H-1,4-benzodiazepine
- 10 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(R)-[(S)-1-phenyl-ethyl]-4-(methylsulfonyl)-1H-1,4-benzodiazepine
- 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(R)-[(S)-1-phenyl-ethyl]-4-(propylsulfonyl)-1H-1,4-benzodiazepine
- 15 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(R)-[(S)-1-phenyl-ethyl]-4-(phenylsulfonyl)-1H-1,4-benzodiazepine
- 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(R)-[(S)-1-phenyl-ethyl]-4-((2-thienyl)-sulfonyl)-1H-1,4-benzodiazepine
- 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(S)-[(S)-1-phenyl-ethyl]-4-(methylsulfonyl)-1H-1,4-benzodiazepine
- 20 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(S)-[(S)-1-phenyl-ethyl]-4-(propylsulfonyl)-1H-1,4-benzodiazepine
- 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(S)-[(S)-1-phenyl-ethyl]-4-(phenylsulfonyl)-1H-1,4-benzodiazepine
- 25 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(S)-[(S)-1-phenyl-ethyl]-4-((2-thienyl)-sulfonyl)-1H-1,4-benzodiazepine
- 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(R)-[(R)-phenylcyclopropyl]-4-(methylsulfonyl)-1H-1,4-benzodiazepine
- 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(R)-[(R)-phenylcyclopropyl]-4-(propylsulfonyl)-1H-1,4-benzodiazepine
- 30 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(R)-[(R)-phenylcyclopropyl]-4-(phenylsulfonyl)-1H-1,4-benzodiazepine
- 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(R)-[(R)-phenylcyclopropyl]-4-((2-thienyl)-sulfonyl)-1H-1,4-benzodiazepine
- 35 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(R)-[(S)-phenylcyclopropyl]-4-(methylsulfonyl)-1H-1,4-benzodiazepine

- 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(R)-[(S)-phenylcyclopropyl]-4-(propylsulfonyl)-1H-1,4-benzodiazepine
7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(R)-[(S)-phenylcyclopropyl]-4-(phenylsulfonyl)-1H-1,4-benzodiazepine
5 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(R)-[(S)-phenylcyclopropyl]-4-((2-thienyl)-sulfonyl)-1H-1,4-benzodiazepine
7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(S)-[(R)-phenylcyclopropyl]-4-(methylsulfonyl)-1H-1,4-benzodiazepine
7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(S)-[(R)-phenylcyclopropyl]-4-(propylsulfonyl)-1H-1,4-benzodiazepine
10 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(S)-[(R)-phenylcyclopropyl]-4-(phenylsulfonyl)-1H-1,4-benzodiazepine
7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(S)-[(R)-phenylcyclopropyl]-4-((2-thienyl)-sulfonyl)-1H-1,4-benzodiazepine
15 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(S)-[(S)-phenylcyclopropyl]-4-(methylsulfonyl)-1H-1,4-benzodiazepine
7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(S)-[(S)-phenylcyclopropyl]-4-(propylsulfonyl)-1H-1,4-benzodiazepine
7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(S)-[(S)-phenylcyclopropyl]-4-(phenylsulfonyl)-1H-1,4-benzodiazepine
20 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(S)-[(S)-phenylcyclopropyl]-4-((2-thienyl)-sulfonyl)-1H-1,4-benzodiazepine
(R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-[(2-(5-(pyridin-2-yl))-thienyl)-sulfonyl]-1H-1,4-benzodiazepine
25 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-[(2-(5-(1,2-isoxazol-3-yl))-thienyl)-sulfonyl]-1H-1,4-benzodiazepine
(R)-7-Cyano-2,3,4,5-tetrahydro-1-(3-(1H-imidazol-2-yl)-propyl)-3-(phenylmethyl)-4-(phenylsulfonyl)-1H-1,4-benzodiazepine
30 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(3-(1H-imidazol-2-yl)-propyl)-3-(phenylmethyl)-4-(methylsulfonyl)-1H-1,4-benzodiazepine
(R)-7-Cyano-2,3,4,5-tetrahydro-1-(3-(1H-imidazol-2-yl)-propyl)-3-(phenylmethyl)-4-(propylsulfonyl)-1H-1,4-benzodiazepine
35 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(3-(1H-imidazol-2-yl)-propyl)-3-(phenylmethyl)-4-((2-thienyl)-sulfonyl)-1H-1,4-benzodiazepine

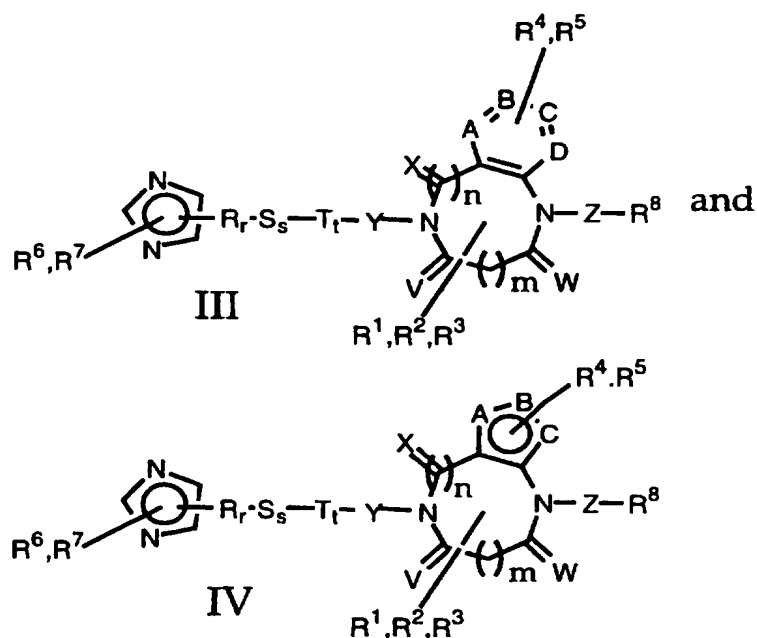
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(2-(1H-imidazol-2-yl)-ethylsulfonyl)-3-(phenylmethyl)-4-(phenylsulfonyl)-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(2-(1H-imidazol-2-yl)-ethylsulfonyl)-3-(phenylmethyl)-4-(methylsulfonyl)-1H-1,4-benzodiazepine
- 5 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(2-(1H-imidazol-2-yl)-ethylsulfonyl)-3-(phenylmethyl)-4-(propylsulfonyl)-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(2-(1H-imidazol-2-yl)-ethylsulfonyl)-3-(phenylmethyl)-4-((2-thienyl)-sulfonyl)-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-
- 10 (phenylmethyl)-4-((1-oxoethyl)-amino)-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(methanesulfonylamino)-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-
- 15 (phenylmethyl)-4-(phenylsulfonylamino)-1H-1,4-benzodiazepine

What is claimed:

1. A compound of the formula



5



- 10 their enantiomers, diastereomers, and pharmaceutically acceptable salts, prodrugs and solvates thereof inhibit farnesyl protein transferase which is an

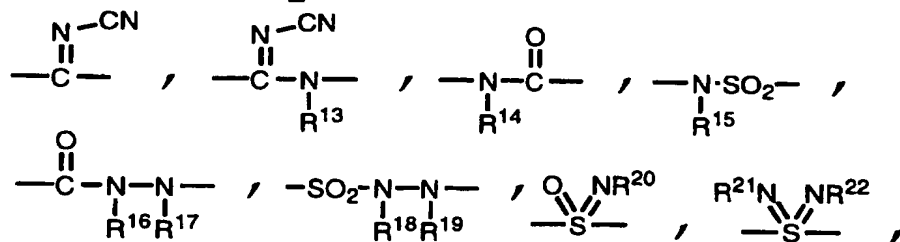
enzyme involved in ras oncogene expression. In formulas I-IV and throughout their specification, the above symbols are defined as follows:

m, n, r, s and t are 0 or 1;

p is 0, 1 or 2;

- 5 V, W and X are selected from the group consisting of oxygen, hydrogen, R¹, R² or R³;

Z and Y are selected from the group consisting of CHR⁹, SO₂, SO₃, CO, CO₂, O, NR¹⁰, SO₂NR¹¹, CONR¹²,



- 10 or Z may be absent;

R⁶, R⁷, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R²⁹, R³⁰, R³¹, R³², R³³, R³⁴, R³⁵, R³⁶, R³⁷, and R³⁸ are selected from the group consisting of hydrogen, lower alkyl, substituted alkyl, aryl, or substituted aryl;

- 15 R⁴, R⁵ are selected from the group consisting of hydrogen, halo, nitro, cyano and U-R²³;

U is selected from the group consisting of sulfur, oxygen, NR²⁴, CO, SO, SO₂, CO₂, NR²⁵CO₂, NR²⁶CONR²⁷, NR²⁸SO₂, NR²⁹SO₂NR³⁰, SO₂NR³¹, NR³²CO, CONR³³, PO₂R³⁴ and PO₃R³⁵ or U is absent;

- 20 R¹, R², and R³ are selected from the group consisting of hydrogen, alkyl, alkoxy carbonyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aralkyl, cycloalkyl, aryl, substituted aryl, heterocyclo, substituted heterocyclo, cyano, carboxy, carbamyl (e.g. CONH₂) or substituted carbamyl further selected from CONH alkyl, CONH aryl, CONH aralkyl or cases where there are two substituents on the nitrogen selected from alkyl, aryl or aralkyl;

R⁸ and R²³ are selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aralkyl, cycloalkyl, aryl, substituted aryl, heterocyclo, substituted heterocyclo;

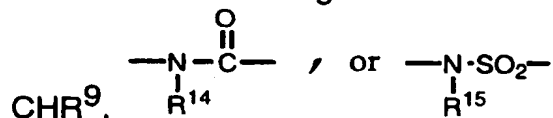
- 30 Any two of R¹, R², and R³ can be joined to form a cycloalkyl group;

R, S and T are selected from the group consisting of CH_2 , CO and $\text{CH}(\text{CH}_2)_p\text{Q}$ wherein Q is $\text{NR}^{36}\text{R}^{37}$, OR^{38} , or CN; and

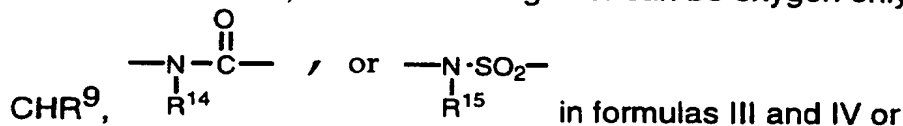
A, B, C and D are carbon, oxygen, sulfur or nitrogen.

with the provisos that

- 5 1. When m is zero then V and W are not both oxygen or
2. W and X together can be oxygen only if Z is either absent, O, NR^{10} ,

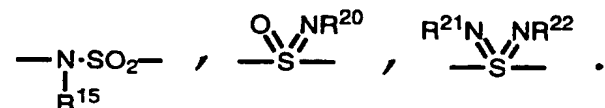


in formulas I and II, and V and X together can be oxygen only if Y is O, NR^{10} ,

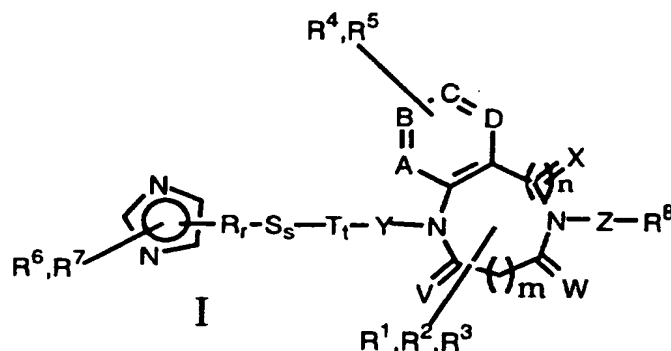


- 10 3. R^{23} may be hydrogen except when U is SO, SO_2 , $\text{NR}^{25}\text{CO}_2$ or $\text{NR}^{28}\text{SO}_2$, or

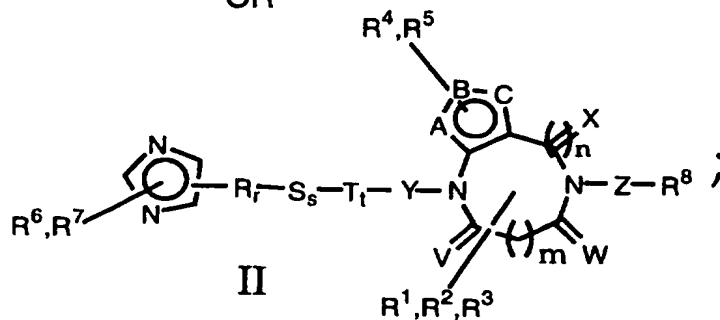
4. R^8 may be hydrogen except when Z is SO_2 , CO_2 , or



2. The compound of claim 1 wherein the compound is selected from the group consisting of



OR



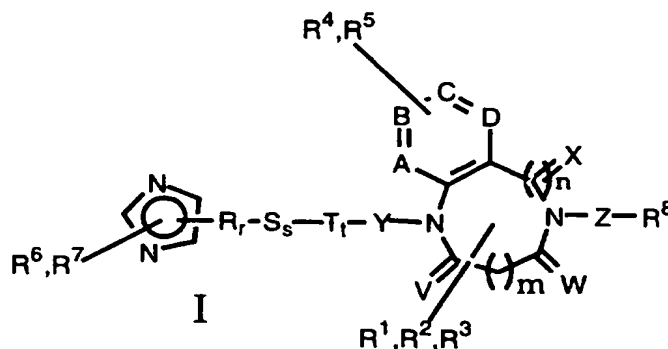
5

3. The compound of claim 2 wherein m is zero and ABCD is a carbocyclic ring.

4. The compound of claim 3 wherein the carbocyclic ring is benzo.

10

5. The compound of claim 1 wherein the compound is of the formula



15

wherein m is zero and ABCD is a carbocyclic ring.

6. The compound of claim 5 wherein the carbocyclic ring is benzo.

5

7. A compound of claim 1 selected from the group consisting of:
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, hydrochloride;
- 8-Chloro-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, hydrochloride;
- 1,2,3,4-tetrahydro-4-[(3H-imidazol-4-yl) methyl]-1-(naphthalen-1-ylcarbonyl)quinoxaline, dihydrochloride;
- 2,3,4,5-Tetrahydro-4-(1H-imidazol-4-yl-methyl)-1-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, dihydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-yl-methyl)-2-methyl-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, hydrochloride;
- 2,3,4,5-Tetrahydro-4-(1-naphthalenylcarbonyl)-1-[[1-(phenylmethyl)-1H-imidazol-5-yl]methyl]-1H-1,4-benzodiazepine, hydrochloride;
- 2,3,4,5-Tetrahydro-(1H-imidazol-4-yl-methyl)-4-(1-naphthalenylsulfonyl)-1H-1,4-benzodiazepine, hydrochloride;
- (S)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-[2-(methylthio)ethyl]-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, hydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-yl-methyl)-N-methyl-N-phenyl-4H-1,4-benzodiazepine-4-carboxamide, hydrochloride;
- 2-[2,3,4,5-Tetrahydro-1-(1H-imidazol-4-yl-methyl)-1H-1,4-benzodiazepin-4-yl]sulfonyl]benzoic acid, methyl ester, hydrochloride;
- 7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, hydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-7-phenyl-1H-1,4-benzodiazepine, hydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-2-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, dihydrochloride;
- 2,3,4,5-Tetrahydro-1-[3-(1H-imidazol-2-yl)propyl]-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, dihydrochloride;
- 1-[3-Amino-3-(1H-imidazol-2-yl)propyl]-2,3,4,5-tetrahydro-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, trihydrochloride;

- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-methyl-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, hydrochloride;
 (S)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-[2-(methylthio)ethyl]-4-(1-naphthalenylmethyl)-1H-1,4-benzodiazepine, hydrochloride;
- 5 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-9-methyl-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, dihydrochloride;
 2,3,4,5-Tetrahydro-4-(1H-imidazol-4-ylmethyl)-9-methyl-1-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, dihydrochloride;
 1-[[2-(2-Aminoethyl)-1H-imidazol-4-yl]methyl]-2,3,4,5-tetrahydro-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, trihydrochloride;
- 10 1-[[2-Aminomethyl)-1H-imidazol-4-yl]methyl]-2,3,4,5-tetrahydro-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, trihydrochloride;
 N-[2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepin-8-yl]acetamide,
- 15 dihydrochloride;
 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-pyrido[2,3-e]-1,4-diazepine, trihydrochloride;
 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-naphtho[2,3-e]-1,4-diazepine, dihydrochloride;
- 20 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-8-nitro-1H-1,4-benzodiazepine, dihydrochloride;
 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-8-amino-1H-1,4-benzodiazepine, dihydrochloride;
 N-[2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepin-8-yl]benzamide,
- 25 dihydrochloride;
 N-[2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepin-8-yl]cyclohexanamide, dihydrochloride;
- 30 2,3,4,5-Tetrahydro-1-[2-(1H-imidazol-4-yl)ethyl]-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, dihydrochloride;
 2,3,4,5-Tetrahydro-1-[2-(1H-imidazol-4-yl)ethyl]-4-(1-naphthalenylcarbonyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
 7-Bromo-2,3,4,5-tetrahydro-1-[2-(1H-imidazol-4-yl)ethyl]-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, dihydrochloride;
- 35 1-[[1-(2-Aminoethyl)-1H-imidazol-5-yl]methyl]-2,3,4,5-tetrahydro-4-(1-naphthalenylcarbonyl)-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride;

- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine-4-carboxylic acid, phenylmethyl ester;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-[2-(trifluoromethoxy)benzoyl]-1H-1,4-benzodiazepine;
- 5 1,2,3,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-N-methyl-N,7-diphenyl-4H-1,4-benzodiazepine-4-carboxamide, dihydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-7-(1-piperidinylsulfonyl)-1H-1,4-benzodiazepine, monohydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-7-pyridin-2-yl-1H-1,4-benzodiazepine, trihydrochloride;
- 10 7-(2-Furanyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, dihydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-7-(2-thienyl)-1H-1,4-benzodiazepine, dihydrochloride;
- 15 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-7-(4-pyridinyl)-1H-1,4-benzodiazepine, trihydrochloride;
- 2,3,4,5-Tetrahydro-1-[3-(1H-imidazol-2-yl)propyl]-4-(1-naphthalenylcarbonyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
- 7-Bromo-2,3,4,5-tetrahydro-4-(1H-imidazol-4-ylmethyl)-1-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, dihydrochloride;
- 20 8-Chloro-2,3,4,5-tetrahydro-4-(1H-imidazol-4-ylmethyl)-1-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, dihydrochloride;
- 2,3,4,5-Tetrahydro-4-(1H-imidazol-4-ylmethyl)-1-(1-naphthalenylcarbonyl)-7-phenyl-1H-1,4-benzodiazepine, hydrochloride;
- 25 2,3,4,5-Tetrahydro-1,4-bis(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylmethyl)-7-phenyl-1H-1,4-benzodiazepine, trifluoroacetate;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-methoxy-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, dihydrochloride;
- 30 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine-7-carboxylic acid, dihydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-5-ylmethyl)-4-(1-naphthalenylcarbonyl)-7-cyclohexyl-1H-1,4-benzodiazepine, 2.5 hydrochloride;
- 35 7-Butyl-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, dihydrochloride;

- 1-[[2-(2-Aminoethyl)-1H-imidazol-4-yl]methyl]-2,3,4,5-tetrahydro-4-(1-naphthalenylcarbonyl)-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride;
 1-[[2-(Aminomethyl)-1H-imidazol-4-yl]methyl]-2,3,4,5-tetrahydro-4-(1-naphthalenylcarbonyl)-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride;
 5 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-8-[N,N-bis(phenyl-methyl)amino]-1H-1,4-benzodiazepine, trihydrochloride;
 N-[2,3,4,5-Tetrahydro-1-(1H-imidazol-4-yl-methyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepin-8-yl]phenylsulfonamide, dihydrochloride;
 10 N-Phenyl-2,3,4,5-tetrahydro-1-(1H-imidazol-4-yl-methyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine-7-carboxamide, dihydrochloride;
 N-[2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepin-8-yl]-3-methylbenzamide,
 15 dihydrochloride;
 N-[2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepin-8-yl]-4-methylbenzamide, dihydrochloride;
 3-Chloro-N-[2,3,4,5-tetrahydro-1-(1H-imidazol-4-yl-methyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepin-8-yl]benzamide,
 20 dihydrochloride;
 7-Bromo-2,3,4,5-tetrahydro-1-[[2-[(dimethylamino)-methyl]-1H-imidazol-4-yl]methyl]-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, dihydrochloride;
 25 7-(4-Chlorophenyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, dihydrochloride;
 7-(3-Aminophenyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, trihydrochloride;
 1-Methyl-N-[2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepin-8-yl]-1H-pyrrole-2-carboxamide, trihydrochloride;
 30 N-[2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepin-8-yl]-3-furancarboxamide, dihydrochloride;
 35 7-(3-Chlorophenyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, dihydrochloride ;

- 2-Methyl-N-[2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepin-8-yl]benzamide, dihydrochloride;
- 5 N-Phenyl-N'-[2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepin-8-yl]urea, dihydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-7-(3-pyridinyl)-1H-1,4-benzodiazepine, trihydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-9-methoxy-4-(1-naphthalenylcarbonyl)-1H-1,4-diazepine, dihydrochloride;
- 10 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-7-phenyl-1H-pyrido[2,3-e]-1,4-diazepine, trihydrochloride;
- (R)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-[2-(methylthio)ethyl]-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, hydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-15 3-(phenylmethyl)-1H-1,4-benzodiazepine, hydrochloride;
- 2,3,4,5-Tetrahydro-3-(2-hydroxyethyl)-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, trifluoroacetate;
- 2,3,4,5-Tetrahydro-4-(1H-imidazol-4-ylmethyl)-3-[2-(methylthio)ethyl]-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, trifluoroacetate;
- 20 (S)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate;
- 4-Acetyl-7-bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, hydrochloride;
- 25 2,3,4,5-Tetrahydro-4-(1H-imidazol-4-ylmethyl)-1-(1-naphthalenylcarbonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, 1.5 hydrochloride;
- 7-Bromo-1,2,3,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4H-1,4-benzodiazepine-4-carboxamide, trifluoroacetate;
- 7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, hydrochloride;
- 30 4-Acetyl-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-3-(phenylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate;
- 4-Acetyl-7-bromo-3-[(4-chlorophenyl)methyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-1H-1,4-benzodiazepine, dihydrochloride;
- 35 4-Acetyl-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-naphtho[2,3-e]-1,4-diazepine, monohydrochloride;

- N-Cyclohexyl-N'-[2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepin-8-yl]urea, dihydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(phenylmethyl)-1H-naphtho[2,3-e]-1,4-diazepine, monohydrochloride;
- 5 2,2-Dimethyl-N-[2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepin-8-yl]propanamide, dihydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylsulfonyl)-7-phenyl-1H-1,4-benzodiazepine, monohydrochloride;
- 10 4-Acetyl-7-bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(2-naphthalenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride;
- 4-Acetyl-7-bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(1-naphthalenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride;
- 7-(2-Chlorophenyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, dihydrochloride;
- 15 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, monohydrochloride;
- 1-Methyl-N-[2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepin-8-yl]-2-piperidinecarboxamide, trihydrochloride;
- 20 N-[2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepin-8-yl]-4-morpholinecarboxamide, dihydrochloride;
- N-[2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepin-8-yl]-3-methylbutanamide, dihydrochloride;
- 25 1,2,3,4-Tetrahydro-4-[(1H-imidazol-4-yl) methyl]-1-(naphthalen-1-ylsulfonyl)quinoxaline, dihydrochloride;
- 1,2,3,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-N,N,7-triphenyl-4H-1,4-benzodiazepine-4-carboxamide, dihydrochloride;
- 30 1,2,3,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4H-naphtho[2,3-e]-1,4-diazepine-4-carboxylic acid, methyl ester, monohydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-[(4-phenyl-1,2,3-thiadiazol-5-yl)carbonyl]-1H-1,4-benzodiazepine, trifluoroacetate;
- 35

- 8-[[[(Cyclohexylamino)carbonyl]amino]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine-4-carboxylic acid, 1,1-dimethylethyl ester;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-8-[[[(4-methylphenyl)sulfonyl]amino]-3-(phenylmethyl)-1H-1,4-benzodiazepine-4-carboxylic acid, 1,1-dimethylethylester;
- 7-Bromo-1,2,3,4-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-5H-1,4-benzodiazepin-5-one, dihydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[1-oxo-3-(1-piperidinyl)propyl]-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-(4-quinolinylcarbonyl)-1H-1,4-benzodiazepine, trihydrochloride;
- 4-[(5-Bromo-3-pyridinyl)carbonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride;
- (S)-4-[2-(Dimethylamino)-1-oxo-3-phenylpropyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride;
- 2,3,4,5-Tetrahydro-4-[4-hydroxy-3-(4-morpholinyl-methyl)benzoyl]-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride;
- (S)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[(1-methyl-2-pyrrolidinyl)carbonyl]-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-[[2-(propylthio)-3-pyridinyl]carbonyl]-1H-1,4-benzodiazepine, trihydrochloride;
- 4-[(2-Chloro-6-methyl-4-pyridinyl)carbonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-[[2-(phenylthio)-3-pyridinyl]carbonyl]-1H-1,4-benzodiazepine, trihydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[[2-(4-methylphenoxy)-3-pyridinyl]carbonyl]-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[(2-methoxy-3-pyridinyl)carbonyl]-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-[(5-phenyl-4-oxazolyl)carbonyl]-1H-1,4-benzodiazepine, dihydrochloride;
- 4-Acetyl-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-[(tetrahydro-3-furanyl)carbonyl]-1H-1,4-benzodiazepine, dihydrochloride;

- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[(2-methoxyethoxy)acetyl]-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[4-(4-morpholinylmethyl)benzoyl]-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[4-(methylsulfonyl)benzoyl]-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[1-oxo-3-(phenylsulfonyl)propyl]-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-(3-pyridinylacetyl)-1H-1,4-benzodiazepine, trihydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-(2-quinoxalinyllcarbonyl)-1H-1,4-benzodiazepine, tetrahydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(4-isoquinolinylcarbonyl)-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride;
- 4-[(2-Chloro-3-pyridinyl)carbonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-(3-pyridinylcarbonyl)-1H-1,4-benzodiazepine, trihydrochloride;
- 4-[(2,6-Dimethoxy-3-pyridinyl)carbonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-(2-pyrazinylcarbonyl)-1H-1,4-benzodiazepine, tetrahydrochloride;
- 4-(2-Ethoxybenzoyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
- 4-[3-(Dimethylamino)benzoyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-[(1-phenylcyclopropyl)carbonyl]-1H-1,4-benzodiazepine, dihydrochloride;
- 4-[(Bicyclo[4.2.0]octa-1,3,5-trien-7-yl)carbonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
- 4-Benzoyl-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
- 4-(2-Chlorobenzoyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
- 4-(2,3-Dichlorobenzoyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;

- N-[2-[[2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepin-4-yl]carbonyl]phenyl]-acetamide, dihydrochloride;
2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(2-phenoxybenzoyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
5 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(2-methoxybenzoyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
4-(2,3-Dimethoxybenzoyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
4-(2,4-Dimethoxybenzoyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
10 4-(2,5-Dimethoxybenzoyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
4-(2,6-Dimethoxybenzoyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
15 4-(2,3-Dihydroxybenzoyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
4-([1,1'-Biphenyl]-2-ylcarbonyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(2-methylbenzoyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
20 4-(2,3-Dimethylbenzoyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
4-(3-Cyanobenzoyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
25 4-(3-Chlorobenzoyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(3-phenoxybenzoyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(3-methoxybenzoyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
30 4-(3,4-Dimethoxybenzoyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
4-(3,5-Dimethoxybenzoyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
35 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(3-methylbenzoyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;

- 4-(1,2-Dioxo-2-phenylethyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
4-[(2-Ethoxy-1-naphthalenyl)carbonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
5 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(2-naphthalenylcarbonyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
4-(Fluorophenylacetyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
4-(Diphenylacetyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
10 2,3,4,5-Tetrahydro-4-(2-hydroxy-1-oxo-2-phenylpropyl)-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1H-indol-2-ylcarbonyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
15 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1H-indol-3-ylcarbonyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1H-indol-5-ylcarbonyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[(1-methyl-1H-indol-2-yl)carbonyl]-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
20 4-(2-Benzofuranylcarbonyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-(3-pyridinylcarbonyl)-1H-1,4-benzodiazepine, N-oxide, dihydrochloride;
25 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-(2-pyridinylcarbonyl)-1H-1,4-benzodiazepine, trihydrochloride;
2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-(2-quinolinylcarbonyl)-1H-1,4-benzodiazepine, trihydrochloride;
2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-(1-isoquinolinylcarbonyl)-1H-1,4-benzodiazepine, trihydrochloride;
30 4-(3-Chloro-2-nitrobenzoyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(2-nitrobenzoyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
35 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(3-methoxy-2-nitrobenzoyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;

- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1H-indol-4-ylcarbonyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
4-[(2,6-Dihydroxy-3-naphthalenyl)carbonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
5 4-(1H-Benzimidazol-5-ylcarbonyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride;
4-(1H-Benzotriazol-5-ylcarbonyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[(4-methoxy-2-quinolinyl)carbonyl]-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride;
10 N-[3-[[2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepin-4-yl]carbonyl]phenyl]-acetamide, dihydrochloride;
2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(2-methyl-1-oxo-2-phenylpropyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
15 4-[2-(Dimethylamino)benzoyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride;
4-(3-Ethoxybenzoyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
2,3,4,5-Tetrahydro-4-(2-hydroxy[1,1'-biphenyl]-3-ylcarbonyl)-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
20 2,3,4,5-Tetrahydro-4-[2-[(2-hydroxyethyl)thio]benzoyl]-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[(2-methoxy-1-naphthalenyl)carbonyl]-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
25 2,3,4,5-Tetrahydro-4-[(2-hydroxy-4-quinolinyl)-carbonyl]-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
2-[[2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepin-4-yl]carbonyl]benzamide, dihydrochloride;
N-(1,1-Dimethylethyl)-2-[[2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepin-4-yl]carbonyl]benzamide, dihydrochloride;
30 N-(4-Fluorophenyl)-N'-[3-[[2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepin-4-yl]carbonyl]phenyl]urea, dihydrochloride;
2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[(3-methyl-4-oxo-2-phenyl-4H-benzopyran-8-yl)carbonyl]-7-phenyl-1H-1,4-benzodiazepine,
35 dihydrochloride;
2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-[3-(trifluoromethoxy)benzoyl]-1H-1,4-benzodiazepine, dihydrochloride;

- 4-(2-Cyanobenzoyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[2-[(4-methylphenyl)sulfonyl]amino]benzoyl]-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-(6-quinolinylcarbonyl)-1H-1,4-benzodiazepine, trihydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-(8-quinolinylcarbonyl)-1H-1,4-benzodiazepine, trihydrochloride;
- 4-(Benzo[b]thiophen-2-ylcarbonyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
- 4-[[4-(Dimethylamino)-1-naphthalenyl]carbonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-(1H-purin-6-ylcarbonyl)-1H-1,4-benzodiazepine, trihydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methoxyphenylacetyl)-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[(5-methyl-1-phenyl-1H-pyrazol-4-yl)carbonyl]-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[2-(2-methylphenyl)-1-oxopropyl]-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-[(tetrahydro-4-phenyl-2H-pyran-4-yl)carbonyl]-1H-1,4-benzodiazepine, dihydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[2-(methylphenylamino)benzoyl]-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-(4-quinolinylcarbonyl)-1H-1,4-benzodiazepine, N-oxide, dihydrochloride;
- N-Methyl-N-(2-pyridinylmethyl)-2-[[2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepin-4-yl]carbonyl]benzamide, trihydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(3-isoquinolinylcarbonyl)-7-phenyl-1H-1,4-benzodiazepine, trihydrochloride;
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[(2-naphthalenylthio)acetyl]-1H-1,4-benzodiazepine, trifluoroacetate (1:2);
- 4-[3-(3,4-Dimethoxyphenyl)-1-oxopropyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate (1:2);

- 4-([1,1'-Biphenyl]-4-ylacetyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate (1:2);
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(2-naphthalenylacetyl)-1H-1,4-benzodiazepine, trifluoroacetate (1:2);
- 5 4-([1,1'-Biphenyl]-2-ylcarbonyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate (1:2);
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[(2-phenyl-4-quinolinyl)carbonyl]-1H-1,4-benzodiazepine, trifluoroacetate (1:3);
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(3-pyridinylacetyl)-1H-1,4-benzodiazepine, trifluoroacetate (1:3);
- 10 4-(9H-Fluoren-9-ylacetyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate (1:2);
- (S)-4-[2-(Dimethylamino)-1-oxo-3-phenylpropyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate (1:3);
- 15 (S)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[(2-oxo-4-phenyl-3-oxazolidinyl)acetyl]-1H-1,4-benzodiazepine, trifluoroacetate (1:2);
- 4-(9-Acridinylcarbonyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate (1:3);
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(3-phenoxybenzoyl)-1H-1,4-benzodiazepine, trifluoroacetate (1:2);
- 20 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]-1H-1,4-benzodiazepine, trifluoroacetate (1:2);
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(4-phenoxybenzoyl)-1H-1,4-benzodiazepine, trifluoroacetate (1:2);
- 25 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(2-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, trifluoroacetate (1:2);
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-oxo-4-phenylbutyl)-1H-1,4-benzodiazepine, trifluoroacetate (1:2);
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[(2-phenoxyphenyl)acetyl]-1H-1,4-benzodiazepine, trifluoroacetate (1:2);
- 30 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[2-[(4-methylphenyl)sulfinyl]benzoyl]-1H-1,4-benzodiazepine, trifluoroacetate (1:2);
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[2-[(phenylmethyl)amino]benzoyl]-1H-1,4-benzodiazepine, trifluoroacetate (1:3);
- 35 1,2,3,5-Tetrahydro-1-(1H-imidazol-4-yl-methyl)-N,N-diphenyl-4H-1,4-benzodiazepine-4-carboxamide, hydrochloride;

- 1,2,3,5-Tetrahydro-1-(1H-imidazol-4-yl-methyl)-a,7-diphenyl-4H-1,4-benzodiazepine-4-acetic acid, methyl ester, hydrochloride;
4-Acetyl-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, hydrochloride;
- 5 (R)-7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, hydrochloride;
(R)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine-7-carbonitrile, monohydrochloride;
(R)-4-Acetyl-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-3-
- 10 (phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride;
7-Bromo-4-[[2-(dimethylamino)ethyl]sulfonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4H-1,4-benzodiazepine, trifluoroacetate (1:2);
2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-[(1,2,3,4-
- 15 tetrahydro-1-quinoliny)carbonyl]-1H-1,4-benzodiazepine, monohydrochloride;
N-Ethyl-1,2,3,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-N,7-diphenyl-4H-1,4-benzodiazepine-4-carboxamide, monohydrochloride;
4-[(2,3-Dihydro-1H-indol-1-yl)carbonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-
- 20 ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, monohydrochloride;
2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(phenylmethyl)-7-(4-pyridinyl)-1H-1,4-benzodiazepine, trihydrochloride;
(R)-4-[[2-(Dimethylamino)ethyl]sulfonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-
- 25 ylmethyl)-7-phenyl-3-(phenylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate (1:1);
[2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepin-8-yl]carbamic acid, cyclohexyl ester, dihydrochloride;
(R)-7-Bromo-2,3,4,5-tetrahydro-1-(1-methyl-1H-imidazol-5-yl)methyl)-4-
- 30 (methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, hydrochloride;
(R)-7-Cyano-2,3,4,5-tetrahydro-1-[(1-methyl-1H-imidazol-5-yl)methyl]-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.
- (R)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-7-phenyl-3-(phenylmethyl)-1H-pyrido[3,2-e]-1,4-diazepine,
- 35 monohydrochloride.
4-[2-(4-Chlorophenyl)-1,2-dioxoethyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, hydrochloride.

- 4-(1,2-Dioxopropyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzodiazepine, hydrochloride.
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[2-(4-nitrophenyl)-1,2-dioxoethyl]-7-phenyl-1H-1,4-benzodiazepine, hydrochloride.
- 5 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[2-(4-methoxyphenyl)-1,2-dioxoethyl]-7-phenyl-1H-1,4-benzodiazepine, hydrochloride.
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-(3,3,3-trifluoro-1,2-dioxopropyl)-1H-1,4-benzodiazepine, trifluoroacetate (1:2).
- (R)-7-Chloro-2,3,4,5-tetrahydro-1-[(1H-imidazol-4-yl)-methyl]-4-
- 10 (methylsulfonyl)-3-(phenylmethyl)-1H-pyrido[3,2-e]-1,4-diazepine, hydrochloride.
- 6,7,8,9-Tetrahydro-5-(1H-imidazol-4-ylmethyl)-8-(1-naphthalenylcarbonyl)-2-phenyl-5H-pyrimido-[5,4-e][1,4]diazepine, monohydrochloride.
- (R)-7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylacetyl)-4-
- 15 (methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.
- (R)-7-Bromo-2,3,4,5-tetrahydro-1-(2-1H-imidazol-4-ylethyl)-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.
- 20 8-[(Cyclohexylcarbonyl)amino]-1,2,3,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4H-1,4-benzodiazepine-4-carboxylic acid, methyl ester, dihydrochloride.
- N-[2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepin-8-yl]-1-
- 25 piperidinecarboxamide, dihydrochloride.
- (R)-7-Cyano-1,2,3,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4H-1,4-benzodiazepine-4-carboxylic acid, ethyl ester, hydrochloride.
- N-[2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-
- 30 (phenylmethyl)-1H-1,4-benzodiazepin-8-yl]cyclohexanecarboxamide, dihydrochloride.
- (R)-7-Cyano-4-[[2-(dimethylamino)ethyl]sulfonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4H-1,4-benzodiazepine, dihydrochloride.
- 35 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[[2-(4-morpholinyl)ethyl]sulfonyl]-3-(phenylmethyl)-4H-1,4-benzodiazepine, dihydrochloride.

- N-[2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(2-methoxy-3-methylbenzoyl)-1H-1,4-benzodiazepin-8-yl]cyclohexanecarboxamide, dihydrochloride.
- 5 8-[(Cyclohexylcarbonyl)amino]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-N-phenyl-1H-1,4-benzodiazepine-4-carboxamide, dihydrochloride.
- N-[2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[(2-methylphenyl)sulfonyl]-1H-1,4-benzodiazepin-8-yl]cyclohexanamide, dihydrochloride.
- 10 N-[2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[(2-methoxyphenyl)carbonyl]-1H-1,4-benzodiazepin-8-yl]cyclohexanamide, dihydrochloride.
- (R)-7-Cyano-1,2,3,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4H-1,4-benzodiazepine-4-sulfonic acid, ethyl ester, hydrochloride.
- 15 (3R)-7-Bromo-1-[cyano(1H-imidazol-4-yl)methyl]-2,3,4,5-tetrahydro-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.
- (3R)-1-[2-Amino-1-(1H-imidazol-4-yl)ethyl]-2,3,4,5-tetrahydro-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.
- 20 (3R)-1-[2-(Dimethylamino)-1-(1H-imidazol-4-yl)ethyl]-2,3,4,5-tetrahydro-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.
- (3R)-1-[2-Amino-1-(1H-imidazol-4-yl)ethyl]-7-bromo-2,3,4,5-tetrahydro-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.
- 25 (3R)-1-[2-(Dimethylamino)-1-(1H-imidazol-4-yl)ethyl]-7-bromo-2,3,4,5-tetrahydro-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.
- 7-Cyano-1,3,4,5-tetrahydro-1-(1-methyl-1H-imidazol-5-ylmethyl)-3-(phenylmethyl)-4-(phenylsulfonyl)-2H-1,4-benzodiazepin-2-one, monohydrochloride.
- 30 7-Cyano-1,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(phenylsulfonyl)-2H-1,4-benzodiazepin-2-one, monohydrochloride.
- 7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(2-phenylethyl)-1H-1,4-benzodiazepine, dihydrochloride.
- 35 7-Bromo-3-[(3-chlorophenyl)methyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-1H-1,4-benzodiazepine, dihydrochloride.

- (R)-7-Bromo-3-(cyclohexylmethyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-1H-1,4-benzodiazepine, dihydrochloride.
7-Bromo-3-[(2-chlorophenyl)methyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-1H-1,4-benzodiazepine, dihydrochloride.
- 5 (S)-7-Bromo-3-(cyclohexylmethyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-1H-1,4-benzodiazepine, dihydrochloride.
7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-[(4-methoxyphenyl)methyl]-4-(methylsulfonyl)-1H-1,4-benzodiazepine, dihydrochloride.
- 10 4-Acetyl-7-bromo-3-[(2-chlorophenyl)methyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.
4-Acetyl-7-bromo-3-[(3-chlorophenyl)methyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.
7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-[(4-
- 15 hydroxyphenyl)methyl]-4-(methylsulfonyl)-1H-1,4-benzodiazepine, dihydrochloride.
(R)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-7-phenyl-3-(3-pyridinylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.
2,3,4,5-Tetrahydro-8-(hydroxymethyl)-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine, dihydrochloride.
- 20 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-8-(phenoxymethyl)-1H-1,4-benzodiazepine, dihydrochloride.
N-Cyclohexyl-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine-8-carboxamide,
- 25 dihydrochloride.
N-(Cyclohexylmethyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-1H-1,4-benzodiazepine-8-carboxamide, dihydrochloride.
2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-
- 30 N-(phenylmethyl)-1H-1,4-benzodiazepine-8-carboxamide, dihydrochloride.
(R)-4-Acetyl-7-[2-[(dimethylamino)methyl]phenyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.
(R)-4-Acetyl-7-cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-
- 35 (phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.
(R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(1-oxobutyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.

- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(2-methyl-1-oxopropyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(2-pyridinylacetyl)-1H-1,4-benzodiazepine, dihydrochloride.
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(2-thienylsulfonyl)-1H-1,4-benzodiazepine, monohydrochloride.
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[(1-methylethyl)sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-[(trifluoromethyl)sulfonyl]-1H-1,4-benzodiazepine, monohydrochloride.
- (R)-7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(propylsulfonyl)-1H-1,4-benzodiazepine, monohydrochloride.
- (R)-7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(phenylsulfonyl)-1H-1,4-benzodiazepine, monohydrochloride.
- (R)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-3-(phenylmethyl)-4-(phenylsulfonyl)-1H-1,4-benzodiazepine, monohydrochloride.
- (R)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-3-(phenylmethyl)-4-(propylsulfonyl)-1H-1,4-benzodiazepine, monohydrochloride.
- (R)-7-Cyano-4-[(4-fluorophenyl)sulfonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.
- (R)-7-Cyano-4-[(3-cyanophenyl)sulfonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[(1-methyl-1H-imidazol-2-yl)sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.
- (R)-4-[(3-Bromophenyl)sulfonyl]-7-cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.
- (R)-N-[5-[[7-cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-

- 1H-1,4-benzodiazepin-4-yl]sulfonyl]-4-methyl-2-thiazolyl]acetamide, dihydrochloride.
- 4-Acetyl-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-7-(4-pyridinyl)-1H-1,4-benzodiazepine, trihydrochloride.
- 5 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(2-phenyl-1,2-dioxoethyl)-7-(4-pyridinyl)-1H-1,4-benzodiazepine, trihydrochloride.
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-(4-pyridinyl)-4-[2-(trifluoromethoxy)benzoyl]-1H-1,4-benzodiazepine, trihydrochloride.
- (R)-2,3,4,5-Tetrahydro-1-[(1-methyl-1H-imidazol-5-yl)methyl]-4-(methylsulfonyl)-7-phenyl-3-(phenylmethyl)-1H-1,4-benzodiazepine.
- 10 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(phenylacetyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.
- 4-(2-Benzothiazolyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1H-1,4-benzazepine, trihydrochloride.
- 15 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-7-(3-pyridinyl)-4-(trifluoroacetyl)-1H-1,4-benzodiazepine, trihydrochloride.
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(phenylmethyl)-7-(3-pyridinyl)-1H-1,4-benzodiazepine, trihydrochloride.
- 7-Bromo-3-[(1,1-dimethylethoxy)methyl]-1,2,3,4-tetrahydro-1-(1H-imidazol-4-ylmethyl)-5H-1,4-benzodiazepin-5-one.
- 20 7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(phenoxy)methyl)-1H-1,4-benzodiazepine, dihydrochloride.
- 7-Bromo-2,3,4,5-tetrahydro-3-(hydroxymethyl)-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-1H-1,4-benzodiazepine, monohydrochloride.
- 25 7-Bromo-3-[(1,1-dimethylethoxy)methyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-1H-1,4-benzodiazepine.
- [7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepin-8-yl]carbamic acid, 2-methylpropyl ester, trihydrochloride.
- 30 [4-Acetyl-7-bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepin-8-yl]carbamic acid, 2-methylpropyl ester.
- N-[4-Acetyl-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepin-8-yl]cyclohexanecarboxamide, dihydrochloride.
- 35 [7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepin-8-yl]carbamic acid, 2-methylpropyl ester.

- (R)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(phenylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine-7-carbonitrile, monohydrochloride.
7-Bromo-1,2,3,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4H-1,4-benzodiazepine-4-acetamide.
- 5 7-Bromo-4-[(dimethylamino)acetyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine.
(R)-7-Bromo-4-(1,2-dioxopropyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate.
(R)-7-Bromo-4-(cyclopropylcarbonyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate.
- 10 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(propylsulfonyl)-1H-1,4-benzodiazepine, monohydrochloride.
7-Bromo-2,3,4,5-tetrahydro-1,4-bis(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.
- 15 7-Bromo-1,2,3,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-N,N-dimethyl-3-(phenylmethyl)-4H-1,4-benzodiazepine-4-sulfonamide, monohydrochloride.
2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine-7-carbonitrile, monohydrochloride.
- 20 (R)-7-Cyano-1,2,3,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-N,N-dimethyl-3-(phenylmethyl)-4H-1,4-benzodiazepine-4-carboxamide, monohydrochloride.
N,N-Diethyl-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine-7-carboxamide, monohydrochloride.
- 25 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-(1-phenyl-1H-tetrazol-5-yl)-1H-1,4-benzodiazepine, monohydrochloride.
(R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(2-pyrazinylcarbonyl)-4H-1,4-benzodiazepine, monohydrochloride.
- 30 (R)-4-[7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4H-1,4-benzodiazepin-4-yl]-4-oxobutanoic acid, methyl ester, monohydrochloride.
(R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(4-morpholinylcarbonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine,
- 35 monohydrochloride.

- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-[[2-(1-pyrrolidinyl)ethyl]sulfonyl]-1H-1,4-benzodiazepine, dihydrochloride.
- (S)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-7-phenyl-3-(3-pyridinylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.
- (R)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-3-(3-pyridinylmethyl)-4-(2-thienylsulfonyl)-1H-1,4-benzodiazepine, dihydrochloride.
- (R)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4-(propylsulfonyl)-3-(3-pyridinylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.
- (R)-7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(2-pyridinylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(phenylmethyl)-7-(2-pyrimidinyl)-1H-1,4-benzodiazepine, dihydrochloride.
- (R)-7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-[(trifluoromethyl)sulfonyl]-1H-1,4-benzodiazepine, monohydrochloride.
- (R)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-3-(phenylmethyl)-4-(trifluoroacetyl)-1H-1,4-benzodiazepine, monohydrochloride.
- (R)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(phenylmethyl)-7-(4-pyridinyl)-1H-1,4-benzodiazepine, dihydrochloride.
- (R)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-7-(4-pyridinyl)-4-(2-thienylsulfonyl)-1H-1,4-benzodiazepine, dihydrochloride.
- (R)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(phenylsulfonyl)-7-(4-pyridinyl)-1H-1,4-benzodiazepine, dihydrochloride.
- (R)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(propylsulfonyl)-7-(4-pyridinyl)-1H-1,4-benzodiazepine, dihydrochloride.
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-[(3,5-dimethyl-isoxazol-4-yl)sulfonyl]-1H-1,4-benzodiazepine, dihydrochloride.
- (R)-7-Cyano-4-[(4-cyanophenyl)sulfonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.

- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-[(2,2,2-trifluoroethyl)sulfonyl]-1H-1,4-benzodiazepine, dihydrochlorid .
- 5 (R)-[(5-Bromo-2-thienyl)sulfonyl]-7-cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[(4-methoxyphenyl)sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.
- 10 N-[[7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-1H-1,4-benzodiazepin-3-yl]methyl]benzamide, dihydrochloride.
- (R)-7-Cyano-1,2,3,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-N,N-dimethyl-3-(phenylmethyl)-4H-1,4-benzodiazepine-4-sulfonamide, hydrochloride.
- 15 (R)-7-Cyano-1,2,3,5-tetrahydro-N,N-dimethyl-1-[(1-methyl-1H-imidazol-5-yl)methyl]-3-(phenylmethyl)-4H-1,4-benzodiazepine-4-sulfonamide, hydrochloride.
- (R)-7-Chloro-2,3,4,5-tetrahydro-1-[(1-methyl-1H-imidazol-5-yl)methyl]-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.
- 20 (R)-7-Chloro-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.
- (R)-7-Chloro-2,3,4,5-tetrahydro-1-[(1-methyl-1H-imidazol-5-yl)methyl]-4-(phenylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine,
- 25 monohydrochloride.
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(pyridin-3-ylmethyl)-4-(methylsulfonyl)-1H-1,4-benzodiazepine, tetrahydrochloride.
- (R)-7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-2-ylmethyl)-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.
- 30 (R)-7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[(1-methyl-1H-imidazol-4-yl)sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, trihydrochloride.
- (R)-7-Chloro-2,3,4,5-tetrahydro-1-(1-methyl-imidazol-5-ylmethyl)-4-[(2-morpholin-4-yl-ethyl)sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine,
- 35 dihydrochloride.

- (R)-7-Chloro-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[(2-morpholin-4-yl-ethyl)sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.
- 5 (R)-7-Chloro-4-[(dimethylamino)sulfonyl]-1-[(1-methyl-1H-imidazol-5-yl)methyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.
- (R)-7-Chloro-2,3,4,5-tetrahydro-1-(1-methyl-imidazol-5-ylmethyl)-4-[(4-methyl-piperidin-4-yl-ethyl)sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.
- 10 (R)-7-Bromo-2,3,4,5-tetrahydro-1-(1-methyl-imidazol-5-ylmethyl)-4-[(4-methyl-piperidin-4-yl-ethyl)sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.
- (R)-7-Cyano-1,2,3,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4H-1,4-benzodiazepine-4-carboxylic acid, isopropyl ester, hydrochloride.
- 15 (R)-7-Bromo-2,3,4,5-tetrahydro-4-[[2-(1H-imidazol-1-yl)ethyl]sulfonyl]-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(propylsulfonyl)-3-(3-pyridinylmethyl)-1H-1,4-benzodiazepine, hydrochloride.
- 20 7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepin-5-one, hydrochloride.
- (R)-7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-1-ylacetyl)-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate.
- 25 1,2,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-2-(2-phenylethyl)-3H-1,4-benzodiazepin-3-one.
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-2-(2-phenylethyl)-1H-1,4-benzodiazepine, monohydrochloride.
- (R)-2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-7-phenyl-3-(4-pyridinylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.
- 30 (R)-2,3,4,5-Tetrahydro-1-(1H-imidazol-2-ylmethyl)-4-(phenylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine-7-carbonitrile, hydrochloride.
- (R)-7-Cyano-1,2,3,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-N,N-dimethyl-3-(3-pyridinylmethyl)-4H-1,4-benzodiazepine-4-carboxamide, dihydrochloride.
- 35 (R)-7-Cyano-1,2,3,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-N,N-dimethyl-3-(3-pyridinylmethyl)-4H-1,4-benzodiazepine-4-sulfonamide, dihydrochloride.

- 4-[(4-Fluorophenyl)sulfonyl]-2,3,4,5-tetrahydro-1-[(1-methyl-1H-imidazol-5-yl)-3-(phenylmethyl)-1H-thieno[2,3-e]-1,4-diazepine, monohydrochloride.
(R)-2,3,4,5-Tetrahydro-1-(1-(4-cyanophenylmethyl)-imidazol-5-ylmethyl)-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine-7-carbonitrile,
5 hydrochloride.
(R)-2,3,4,5-Tetrahydro-1-(1-(4-cyanophenylmethyl)-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine-7-carbonitrile, hydrochloride.
(R)-4-Benzoyl-7-cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.
10 (R)-7-Cyano-2,3,4,5-tetrahydro-1-[(1-methyl-1H-imidazol-5-yl)methyl]-3-(pyridin-3-ylmethyl)-4-(methylsulfonyl)-1H-1,4-benzodiazepine, dihydrochloride.
(R)-7-Cyano-2,3,4,5-tetrahydro-1-[(1-methyl-1H-imidazol-5-yl)methyl]-3-(pyridin-3-ylmethyl)-4-(propylsulfonyl)-1H-1,4-benzodiazepine,
15 trihydrochloride.
(R)-7-Cyano-2,3,4,5-tetrahydro-1-[(1H-imidazol-4-yl)methyl]-3-(pyridin-3-ylmethyl)-4-(phenylsulfonyl)-1H-1,4-benzodiazepine, dihydrochloride.
2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-7-phenyl-
20 3-(phenylmethyl)-1H-1,4-benzodiazepine.
1,2,3,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-N-(1-naphthalenyl)-7-phenyl-4H-1,4-benzodiazepine-4-carboxamide, monohydrochloride.
(S)-7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, hydrochloride.
25 N-[2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(2,3-dimethylbenzoyl)-1H-1,4-benzodiazepin-8-yl]cyclohexanecarboxamide, dihydrochloride.
(R)-7-Cyano-N-[2-(dimethylamino)ethyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-N-methyl-3-(phenylmethyl)-1H-1,4-benzodiazepine-4-carboxamide, trifluoroacetate (1:2).
30 7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-2-oxo-3-(phenylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate.
(R)-7-Cyano-4-(2-furanylcarbonyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate (1:1).
(R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[(4-
35 nitrophenyl)sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate.

- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[[4-(4-methyl-1-piperazinyl)phenyl]sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate.
- 5 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[[4-(4-dimethylamino)phenyl]sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, trifluoroacetate.
- (R)-7-Bromo-4-[[2-(dimethylamino)ethyl]sulfonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4H-1,4-benzodiazepine, dihydrochloride.
- 10 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(3-pyridinylsulfonyl)-1H-1,4-benzodiazepine, trihydrochloride.
- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.
- 15 (R)-7-Bromo-2,3,4,5-tetrahydro-1-[(1-methyl-1H-imidazol-4-yl)methyl]-4-(methylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.
- (R)-4-[[3-(Dimethylamino)propyl]sulfonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.
- 20 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, trihydrochloride.
- 4-Butyl-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, trihydrochloride.
- (R)-7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[[2-(4-morpholinyl)ethyl]sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.
- 25 (R)-7-Bromo-2,3,4,5-tetrahydro-1-[(1-methyl-1H-imidazol-5-yl)methyl]-4-[[2-(4-morpholinyl)ethyl]sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.
- 30 (R)-7-Cyano-1-(1H-imidazol-4-ylmethyl)-4-(4-morpholinylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.
- (R)-7-Cyano-1-[(1-methyl-1H-imidazol-5-yl)methyl]-4-[(4-morpholinyl)sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.
- 35 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[(4-aminophenyl)sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, hydrochloride.

- 2,3,4,5-Tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-[(4-pyridylthio)acetyl]-7-phenyl-1H-1,4-benzodiazepine, dihydrochloride.
- N-(4-Chlorophenyl)-N'-cyano-1,2,3,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-1,4-benzodiazepine-4-imidamide,
- 5 monohydrochloride.
- 4-Acetyl-7-bromo-1,2,4,5,1',3'-hexahydro-1-(1H-imidazol-4-ylmethyl)spiro[3H-1,4-benzodiazepine-3,2'-[2H]indene], dihydrochloride.
- 7-Bromo-4-[3-(dimethylamino)-1-oxopropyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine,
- 10 trifluoroacetate (1:1).
- (R)-2,3,4,5-Tetrahydro-1-(1-methyl-1H-imidazol-5-ylmethyl)-4-(phenylsulfonyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine-7-carbonitrile, monohydrochloride.
- 2,3,4,5-Tetrahydro-1-[(1-methyl-1H-imidazol-5-yl)-methyl]-4-(methylsulfonyl)-7-phenyl-3-(pyridin-3-yl-methyl)-1H-1,4-benzodiazepine,
- 15 hydrochloride (1:1.5), trifluoroacetate (1:0.75) salt.
- 4-[4-(Fluorophenyl)sulfonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-2-(2-phenylethyl)-1H-1,4-benzodiazepine, monohydrochloride.
- 7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-yl-methyl)-4-(methyl-sulfonyl)-2-(2-phenylethyl)-1H-1,4-benzodiazepine, monohydrochloride.
- 20 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1-methyl-1H-imidazol-5-ylmethyl)-4-[[2-(1-morpholinyl)ethyl]sulfonyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, dihydrochloride.
- (R)-7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(4-bromophenylmethyl)-1H-1,4-benzodiazepine, hydrochloride.
- 25 (R)-7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(methylsulfonyl)-3-(thiazol-4-ylmethyl)-1H-1,4-benzodiazepine, hydrochloride.
- (R)-7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(propylsulfonyl)-3-(thiazol-4-ylmethyl)-1H-1,4-benzodiazepine, hydrochloride.
- 30 (R)-7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(propylsulfonyl)-3-(4-bromophenylmethyl)-1H-1,4-benzodiazepine, hydrochloride.
- (R)-7-Bromo-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(pyridin-3-ylmethyl)-4-(methylsulfonyl)-1H-1,4-benzodiazepine, trihydrochloride.
- 35 (R)-7-Bromo-2,3,4,5-tetrahydro-1-(1H-1-methyl-imidazol-5-ylmethyl)-3-(pyridin-3-ylmethyl)-4-(methylsulfonyl)-1H-1,4-benzodiazepine, dihydrochloride.

- 1,2,3,4-Tetrahydro-7-bromo-4-[(1H-imidazol-4-yl)methyl]-2-phenylmethyl-1-(phenyl-methyloxycarbonyl)quinoxaline, hydrochloride.
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-(phenylsulfonyl)-3-(4-cyanophenylmethyl)-1H-1,4-benzodiazepine, hydrochloride.
- 5 (R)-7-Cyano-4-[(N-methyl-N-phenylmethyl)aminosulfonyl]-1-[(1H-imidazol-4-yl)methyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.
- (R)-7-Cyano-4-[N-(tetrahydroisoquinolyl)sulfonyl]-1-[(1H-imidazol-4-yl)methyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-4-
- 10 (phenylsulfonyl)-3-(2-thienylmethyl)-1H-1,4-benzodiazepine, hydrochloride.
- cis-2,3,4,5-Tetrahydro-1,5-bis(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,5-benzodiazepine-2-carboxylic acid ethyl ester, trifluoroacetate (1:2).
- (R)-7-Cyano-4-[(N-piperidyl)sulfonyl]-1-[(1H-imidazol-4-yl)methyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine, monohydrochloride.
- 15 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-1-methyl-imidazol-5-ylmethyl)-3-(phenylmethyl)-4-(2-thienylsulfonyl)-1H-1,4-benzodiazepine, hydrochloride.
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(pyridin-3-ylmethyl)-4-[[2-(dimethylamino)ethyl]sulfonyl]-1H-1,4-benzodiazepine,
- 20 trihydrochloride.
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-1-methyl-imidazol-5-ylmethyl)-3-(phenylmethyl)-4-(propylsulfonyl)-1H-1,4-benzodiazepine, hydrochloride.
- N-(Cyano)-N'-methyl-1,2,3,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-7-phenyl-4H-1,4-benzodiazepine-4-imidamide, hydrochloride.
- 25 (R)-7-Cyano-4-[(2-nitrophenyl)sulfonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenyl-methyl)-1H-1,4-benzodiazepine, hydrochloride.
- (R)-7-Cyano-4-[(4-methyl-phenyl)sulfonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, hydrochloride.
- 30 (R)-7-Cyano-4-(butylsulfonyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, hydrochloride.
- (R)-7-Cyano-4-[(2-trifluoro-methylphenyl)sulfonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, hydrochloride.
- 35 (R)-7-Cyano-4-[(2-trifluoromethoxyphenyl)sulfonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, hydrochloride.

- (R)-7-Cyano-4-[(2-methoxy-carbonylphenyl)sulfonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, hydrochloride.
- 5 (R)-7-Cyano-4-[(2-methyl-sulfonylphenyl)sulfonyl]-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-1,4-benzodiazepine, hydrochloride.
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(((4-methylsulfonyl)-phenyl)-sulfonyl)-1H-1,4-benzodiazepine
- 10 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(((4-trifluoromethyl)-phenyl)-sulfonyl)-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-((3-methoxypropyl)-sulfonyl)-1H-1,4-benzodiazepine
- 15 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-((3,4-dimethoxyphenyl)-sulfonyl)-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-((4-fluorophenyl)methyl)-4-(phenylsulfonyl)-1H-1,4-benzodiazepine
- (R)-7-Cyano-4-[(N-cyclopropylmethyl-N-propyl)-aminosulfonyl]-1-[(1H-imidazol-4-yl)methyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine
- 20 (R)-7-Cyano-4-[(N,N-(dibutylamino))-sulfonyl]-1-[(1H-imidazol-4-yl)methyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine
- (R)-7-Chloro-4-(methanesulfonyl)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-pyrido[3,4-e]-1,4-diazepine
- 25 1,2,3,4-Tetrahydro-7-bromo-4-[(1H-imidazol-4-yl)methyl]-2-phenylmethyl-1-(methylsulfonyl)quinoxaline
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-((imidazol-4-yl)methylsulfonyl)-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-((2-thienyl)methyl)-4-(propylsulfonyl)-1H-1,4-benzodiazepine
- 30 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-((2-thienyl)methyl)-4-((2-thienyl)-sulfonyl)-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-((3-methylthiopropyl)-sulfonyl)-1H-1,4-benzodiazepine
- 35 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(((3-methylthio)-propyl)-sulfonyl)-1H-1,4-benzodiazepine

- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(((3-methylsulfonyl)-propyl)-sulfonyl)-1H-1,4-benzodiazepine
- 5 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-((2-methylpropyl)-sulfonyl)-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(cyclopentylsulfonyl)-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-((4,4,4-trifluorobutyl)-sulfonyl)-1H-1,4-benzodiazepine
- 10 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-((phenylmethyl)-sulfonyl)-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-[[2-(5-(N-benzoyl)-aminomethyl)-thienyl]-sulfonyl]-1H-1,4-benzodiazepine
- 15 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-[[2-(1-(3-chloro-5-methyl-pyridin-2-yl))-pyrrolyl]-sulfonyl]-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-((4-carboxyphenyl)-sulfonyl)-1H-1,4-benzodiazepine
- 20 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(((3-methyl-1,2,4-oxadiazol-5-yl)-phenyl)-sulfonyl]-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-((2,5-dimethoxyphenyl)-sulfonyl)-1H-1,4-benzodiazepine
- 25 (R)-7-Cyano-4-[(N-tetrahydroquinolinyl)sulfonyl]-1-[(1H-imidazol-4-yl)methyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine
- (R)-7-Cyano-4-[(N,N-bis-[1-(2-methylpropyl)amino]-sulfonyl)-1-[(1H-imidazol-4-yl)methyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine
- (R)-7-Cyano-4-[(N-methyl-N-phenyl)aminosulfonyl]-1-[(1H-imidazol-4-yl)methyl]-3-(phenylmethyl)-1H-1,4-benzodiazepine
- 30 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(2-(2,6-dimethylphenyl)-ethyl)-4-(methylsulfonyl)-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1-(N-phthalimidoethyl)-imidazol-5-ylmethyl)-3-(phenylmethyl)-4-(methylsulfonyl)-1H-1,4-benzodiazepine
- 35 (R)-7-Cyano-2,3,4,5-tetrahydro-1-[(2-(N,N-dimethylamino)-ethyl)-imidazol-5-ylmethyl]-3-(phenylmethyl)-4-(methylsulfonyl)-1H-1,4-benzodiazepine

- (R)-7-Cyano-2,3,4,5-tetrahydro-1-[(2-aminoethyl)-imidazol-5-ylmethyl]-3-(phenylmethyl)-4-(methylsulfonyl)-1H-1,4-benzodiazepine
- (R)-7-Bromo-4-(methanesulfonyl)-2,3,4,5-tetrahydro-1-[(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-thieno[2,3-e]-1,4-diazepine
- 5 (R)-7-Bromo-4-(methanesulfonyl)-2,3,4,5-tetrahydro-1-[(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-thieno[3,2-e]-1,4-diazepine
- (R)-4-(methanesulfonyl)-2,3,4,5-tetrahydro-1-[(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-1H-8-oxo-pyrimidino[4,5-e]-1,4-diazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-((4-(2-methoxyethoxy)-phenyl)methyl)-4-(phenylsulfonyl)-1H-1,4-benzodiazepine
- 10 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-((4-(2-(dimethylamino)-ethoxy)-phenyl)methyl)-4-(phenylsulfonyl)-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylsulfonyl)-3-(phenylmethyl)-4-(methylsulfonyl)-1H-1,4-benzodiazepine
- 15 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylsulfonyl)-3-(phenylmethyl)-4-(propylsulfonyl)-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylsulfonyl)-3-(phenylmethyl)-4-(phenylsulfonyl)-1H-1,4-benzodiazepine
- 20 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylsulfonyl)-3-(phenylmethyl)-4-(2-thienylsulfonyl)-1H-1,4-benzodiazepine
- 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(R)-[(R)-1-phenylethyl]-4-(methylsulfonyl)-1H-1,4-benzodiazepine
- 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(R)-[(R)-1-phenylethyl]-4-(propylsulfonyl)-1H-1,4-benzodiazepine
- 25 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(R)-[(R)-1-phenylethyl]-4-(phenylsulfonyl)-1H-1,4-benzodiazepine
- 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(R)-[(R)-1-phenylethyl]-4-((2-thienyl)-sulfonyl)-1H-1,4-benzodiazepine
- 30 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(S)-[(R)-1-phenylethyl]-4-(methylsulfonyl)-1H-1,4-benzodiazepine
- 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(S)-[(R)-1-phenylethyl]-4-(propylsulfonyl)-1H-1,4-benzodiazepine
- 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(S)-[(R)-1-phenylethyl]-4-(phenylsulfonyl)-1H-1,4-benzodiazepine
- 35 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(S)-[(R)-1-phenylethyl]-4-((2-thienyl)-sulfonyl)-1H-1,4-benzodiazepine

- 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(R)-[(S)-1-phenyl-ethyl]-4-(methylsulfonyl)-1H-1,4-benzodiazepine
- 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(R)-[(S)-1-phenyl-ethyl]-4-(propylsulfonyl)-1H-1,4-benzodiazepine
- 5 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(R)-[(S)-1-phenyl-ethyl]-4-(phenylsulfonyl)-1H-1,4-benzodiazepine
- 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(R)-[(S)-1-phenyl-ethyl]-4-((2-thienyl)-sulfonyl)-1H-1,4-benzodiazepine
- 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(S)-[(S)-1-phenyl-ethyl]-4-(methylsulfonyl)-1H-1,4-benzodiazepine
- 10 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(S)-[(S)-1-phenyl-ethyl]-4-(propylsulfonyl)-1H-1,4-benzodiazepine
- 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(S)-[(S)-1-phenyl-ethyl]-4-(phenylsulfonyl)-1H-1,4-benzodiazepine
- 15 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(S)-[(S)-1-phenyl-ethyl]-4-((2-thienyl)-sulfonyl)-1H-1,4-benzodiazepine
- 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(R)-[(R)-phenylcyclopropyl]-4-(methylsulfonyl)-1H-1,4-benzodiazepine
- 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(R)-[(R)-phenylcyclopropyl]-4-(propylsulfonyl)-1H-1,4-benzodiazepine
- 20 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(R)-[(R)-phenylcyclopropyl]-4-(phenylsulfonyl)-1H-1,4-benzodiazepine
- 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(R)-[(R)-phenylcyclopropyl]-4-((2-thienyl)-sulfonyl)-1H-1,4-benzodiazepine
- 25 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(R)-[(S)-phenylcyclopropyl]-4-(methylsulfonyl)-1H-1,4-benzodiazepine
- 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(R)-[(S)-phenylcyclopropyl]-4-(propylsulfonyl)-1H-1,4-benzodiazepine
- 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(R)-[(S)-phenylcyclopropyl]-4-(phenylsulfonyl)-1H-1,4-benzodiazepine
- 30 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(R)-[(S)-phenylcyclopropyl]-4-((2-thienyl)-sulfonyl)-1H-1,4-benzodiazepine
- 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(S)-[(R)-phenylcyclopropyl]-4-(methylsulfonyl)-1H-1,4-benzodiazepine
- 35 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(S)-[(R)-phenylcyclopropyl]-4-(propylsulfonyl)-1H-1,4-benzodiazepine

- 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(S)-[(R)-phenylcyclopropyl]-4-(phenylsulfonyl)-1H-1,4-benzodiazepine
- 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(S)-[(R)-phenylcyclopropyl]-4-((2-thienyl)-sulfonyl)-1H-1,4-benzodiazepine
- 5 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(S)-[(S)-phenylcyclopropyl]-4-(methylsulfonyl)-1H-1,4-benzodiazepine
- 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(S)-[(S)-phenylcyclopropyl]-4-(propylsulfonyl)-1H-1,4-benzodiazepine
- 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(S)-[(S)-phenylcyclopropyl]-4-(phenylsulfonyl)-1H-1,4-benzodiazepine
- 10 7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(S)-[(S)-phenylcyclopropyl]-4-((2-thienyl)-sulfonyl)-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-[(2-(5-(pyridin-2-yl))-thienyl)-sulfonyl]-1H-1,4-
- 15 benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-[(2-(5-(1,2-isoxazol-3-yl))-thienyl)-sulfonyl]-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(3-(1H-imidazol-2-yl)-propyl)-3-(phenylmethyl)-4-(phenylsulfonyl)-1H-1,4-benzodiazepine
- 20 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(3-(1H-imidazol-2-yl)-propyl)-3-(phenylmethyl)-4-(methylsulfonyl)-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(3-(1H-imidazol-2-yl)-propyl)-3-(phenylmethyl)-4-(propylsulfonyl)-1H-1,4-benzodiazepine
- 25 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(3-(1H-imidazol-2-yl)-propyl)-3-(phenylmethyl)-4-((2-thienyl)-sulfonyl)-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(2-(1H-imidazol-2-yl)-ethylsulfonyl)-3-(phenylmethyl)-4-(phenylsulfonyl)-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(2-(1H-imidazol-2-yl)-ethylsulfonyl)-3-
- 30 (phenylmethyl)-4-(methylsulfonyl)-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(2-(1H-imidazol-2-yl)-ethylsulfonyl)-3-(phenylmethyl)-4-(propylsulfonyl)-1H-1,4-benzodiazepine
- (R)-7-Cyano-2,3,4,5-tetrahydro-1-(2-(1H-imidazol-2-yl)-ethylsulfonyl)-3-
- (phenylmethyl)-4-((2-thienyl)-sulfonyl)-1H-1,4-benzodiazepine
- 35 (R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-((1-oxoethyl)-amino)-1H-1,4-benzodiazepine

(R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(methanesulfonylamino)-1H-1,4-benzodiazepine
(R)-7-Cyano-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(phenylsulfonylamino)-1H-1,4-benzodiazepine

5

8. A method of inhibiting farnesyl protein transferase which comprises administering to a mammalian subject an effective farnesyl protein transferase inhibiting amount of a compound of Claim 1.

10

9. A method of inhibiting prenyl transferases which comprises administering to a mammalian subject an effective prenyl transferase inhibiting amount of a compound of Claim 1.

15

10. A method of inhibiting tumors which comprises administering to a mammalian subject an effective tumor inhibiting amount of a compound of Claim 1.

20

11. A method of treating diseases associated with signal transduction pathways operating through Ras which comprises administering to a mammalian subject an amount of a compound of Claim 1 effective for treating said diseases.

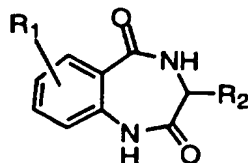
25

12. A method of treating diseases associated with proteins that are post-translationally modified by the enzyme farnesyl protein transferase which comprises administering to a mammalian subject an amount of a compound of Claim 1 effective for treating said diseases.

30

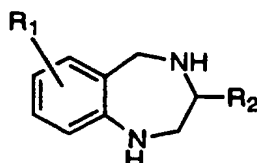
13. A method of treating disease associated with proteins that are post-translationally modified by the enzymes geranylgeranyl protein transferase which comprises administering to a mammalian subject an amount of a compound of Claim 1 effective for treating said diseases.

14. A compound of the formula



5 wherein R₁ is selected from Cl, Br, phenyl, pyridyl or cyano and R₂ is selected from substituted aralkyl or substituted heterocycloalkyl.

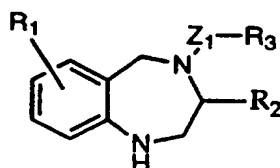
15. A compound of the formula



10

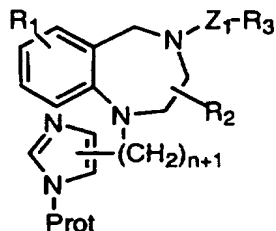
wherein R₁ is selected from Cl, Br, phenyl, pyridyl or cyano and R₂ is selected from substituted aralkyl or substituted heterocycloalkyl.

15 16. A compound of the formula



20 wherein R₁ is selected from Cl, Br, phenyl, pyridyl or cyano; R₂ is selected from substituted aralkyl or substituted heterocycloalkyl; R₃ is selected from substituted alkyl, substituted aryl or substituted heterocyclo; Z₁ is selected from CO, SO₂, CO₂, CONHR₅, SO₃, SO₂NR₅, C(NCN)NR₅; R₅ is selected from hydrogen, lower alkyl, substituted alkyl, aryl or substituted aryl.

17. A compound of the formula



- 5 wherein R₁ is selected from Cl, Br, phenyl, pyridyl or cyano; R₂ is selected from substituted aralkyl or substituted heterocycloalkyl; R₃ is selected from substituted alkyl, substituted aryl or substituted heterocyclo; Z₁ is selected from CO, SO₂, CO₂, CONHR₅, SO₃, SO₂NR₅, or C(NCN)NR₅, Prot is triphenylmethyl or Boc, R₅ is selected from hydrogen, lower alkyl, substituted
- 10 alkyl, aryl or substituted aryl.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/02920

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07D 403/06; A61K 31/55

US CL :514/221; 540, 506, 569, 573

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/221; 540, 506, 569, 573

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CHEMICAL ABSTRACTS 1, 4 Benzodiazepine Vol. 51 —> Vol. 124 (1957 —> June 1966)

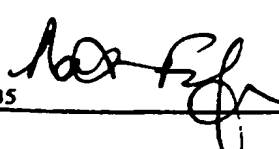
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,441,952 A (CLAREMON ET AL.) 15 August 1995 (15.08.95) see the entire document.	1-17

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* "A" document defining the general state of the art which is not considered to be of particular relevance	*T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier document published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"G" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 14 MAY 1997	Date of mailing of the international search report 09.07.1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer ROBERT T. BOND aco  Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application N .
PCT/US97/02920

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☒

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/02920

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

- I. Claims 1-7 (final products) claims 14-17 (intermediates) and claim 8 (first method of use)
- II. Claim 9 (second method of use).
- III. Claim 10 (third method of use).
- IV. Claim 11 (fourth method of use).
- V. Claim 12 (fifth method of use).
- VI. Claim 13 (sixth method of use).

There is no unity of invention between the various methods of use since each method treats a different disease and the result of each method is different. Accordingly, the claims are not so linked by a special technical within the meaning of PCT Rule 13.2 so as to form a single inventive concept.

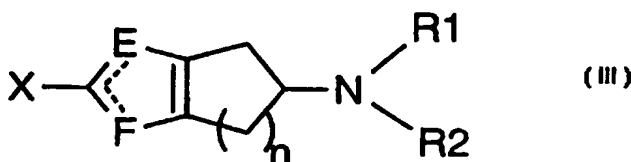
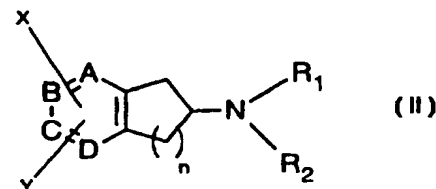
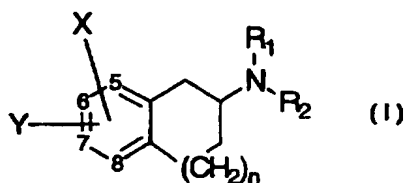


INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: C07C 311/05, 311/18, C07D 233/84, C07C 233/78, 255/57, C07D 261/10, C07C 235/84, 275/30, 275/38, C07D 209/70, A61K 31/18, 31/415, 31/165, 31/275, 31/42, 31/17, 31/40	A1	(11) International Publication Number: WO 97/45403 (43) International Publication Date: 4 December 1997 (04.12.97)
(21) International Application Number: PCT/US97/07650 (22) International Filing Date: 12 May 1997 (12.05.97) (30) Priority Data: 60/018,794 31 May 1996 (31.05.96) US (71) Applicant (for all designated States except US): PHARMACIA & UPJOHN COMPANY [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): HAADSMAN- SVENSSON, Susanne, R. [US/US]; 4318 Squire Heath Lane, Portage, MI 49002 (US). CLEEK, Kerry, Anne [US/US]; 5219 Deerland Street, Kalamazoo, MI 49004 (US). LIN, Chiu-Hong [US/US]; 3720 Pinetree, Portage, MI 49002 (US). LEIBY, Jeffrey, A. [US/US]; 3004 North Westnedge, Kalamazoo, MI 49004 (US). DARLINGTON, William, H. [US/US]; 4524 Moonlite Street, Kalamazoo, MI 49009 (US). ROMERO, Arthur, G. [US/US]; 6629 Morningstar Way, Kalamazoo, MI 49009 (US).	(74) Agent: CORNEGLIO, Donald, L.; Pharmacia & Upjohn Com- pany, Intellectual Property Legal Services, 301 Henrietta Street, Kalamazoo, MI 49001 (US). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report.	

(54) Title: ARYL SUBSTITUTED CYCLIC AMINES AS SELECTIVE DOPAMINE D3 LIGANDS**(57) Abstract**

Compounds and their pharmaceutically acceptable salts suitable for treating central nervous system disorders associated with the dopamine D3 receptor activity of structural Formula (I) where X and Y are at the 5, 6, or 7 position wherein i) n is 1 then X is (CH₂)_mCONR₄R₅, (CH₂)_mSO₂R₃, (CH₂)_mSO₂NR₄R₅, (CH₂)_mNR₄CONHR₅, (CH₂)_mNHSO₂R₃, (CH₂)_mNHCOR₃, or C(O)R₄ (where m is 0 or 1, except that where m is 0, the Y is not hydrogen or halogen); and Y is R₄,



(CH₂)_pCONR₄R₅, (CH₂)_pCN, (CH₂)_pSO₂NR₄R₅, OR₆, (CH₂)_pSO₂R₃, (CH₂)_pNHSO₂R₃, halogen or (CH₂)_pNHCOR₃ (where p is 0 or 1); ii) n is 0 or 1 then X and Y are in *ortho*-positions relative to each other and are jointly: a) -C(O)NR₁₀C(O)-, b) -C(O)NR₄(CH₂)_nNR₁₀C(O)- (where x is 0 or 1), c) -CH₂NR₁₀C(O)-, d) -(CH₂)₂NR₁₀C(O)-, e) -CH₂C(O)NR₁₀-, f) -N(R₃)-C(O)-N(R₃)-, g) -N(R₃)-C(O)-O-, h) -N=C(R₇)-N(R₃)-, or j) -CH₂N(R₈)CH₂-; or iii) n is 0 and Y is OR₉ then X is (CH₂)_mCONR₄R₅, (CH₂)_mSO₂NR₄R₅, (CH₂)_mNR₄CONHR₅, (CH₂)_mSO₂R₃, (CH₂)_mNHSO₂R₃ or (CH₂)_mNHCOR₃, C(O)R₄ (where m is 0 or 1). A compound of structural Formula (II) or its pharmaceutically acceptable salts where one of A, B, C, or D is nitrogen and remaining positions are CH; n is 1 or 2; X and Y are: i) substituted at positions A, B, C, or D wherein X is (CH₂)_mCONR₄R₅, (CH₂)_mCN, (CH₂)_mSO₂NR₄R₅, OSO₂R₃, (CH₂)_mNR₄CONHR₅, (CH₂)_mSO₂R₃, (CH₂)_mNHSO₂R₃ or (CH₂)_mNHCOR₃, C(O)R₄ (where m is 0 or 1, except that where m is 0, Y is not hydrogen or halogen); and Y is R₄, (CH₂)_pCONR₄R₅, (CH₂)_pCN, (CH₂)_pSO₂NR₄R₅, OR₆, OSO₂R₃, (CH₂)_pSO₂R₃, (CH₂)_pNHSO₂R₃, halogen or (CH₂)_pNHCOR₃ (where p is 0 or 1); or ii) jointly in an *ortho*-positions relative to each other and are: -C(O)NR₄C(O)-, -CH₂NR₄C(O)-, -CH₂C(O)NR₄- or -CH₂N(R₄)CH₂-. A compound of structural Formula (III) or its pharmaceutically acceptable salts wherein one of E or F is N and the other is S; n is 1 or 2. The R₁₋₁₀ groups for structural Formula (I), (II) and (III) are as defined above.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LJ	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

ARYL SUBSTITUTED CYCLIC AMINES AS SELECTIVE DOPAMINE D3 LIGANDS

BACKGROUND OF THE INVENTION

The subject invention is directed toward aryl substituted cyclic amines for the
5 treatment of CNS diseases such as schizophrenia, Parkinson's disease, tardive
dyskinesia, obsessive compulsive disorder, depression, and anxiety
that preferentially bind to the dopamine D3 receptor. The dopamine D3 receptor
was recently cloned by Sokoloff et al.. (Nature, 347, 146 (1990)). It was
hypothesized that this receptor subtype is of importance for the action of
10 anti-psychotics. Interestingly, this receptor shows a relatively high abundance in
brain regions associated with emotional and cognitive functions.

Compounds with this profile may be useful in treating CNS disorders, e.g.
schizophrenia, mania, depression, geriatric disorders, drug abuse and addiction,
Parkinson's disease, anxiety disorders, sleep disorders, circadian rhythm disorders
15 and dementia.

Information Disclosure Statement:

PCT Patent Publication No. WO90/07490 describes 2-aminotetralins and
2-aminoindans with aromatic substitution with an OCH₃ or OH in conjunction with
a Br group.

20 PCT Patent Publication No. WO95/04713 describes 2-aminoindans which bind
to the dopamine D3 receptor.

PCT Patent Application No. PCT/US96/00020 describes 2-aminoindans having
sulfonamide substitution on the benzene ring and useful for treating schizophrenia.

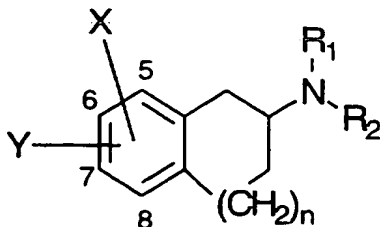
25 US 4,968,679 discloses 2-aminotetralins having a substitution at the 8-
position which are serotonin agonist/antagonist.

PJMurry, Novel 6-substituted 2-Aminotetralins, *Bioorg. & Med. Chem. Lett.*
1996, 403 describes compounds having dopamine D3 receptor selectivity that have
the benzene ring substituted with 5-methoxy and 6-arylethyl and others with
6-CH₂SO₂(4-methoxyphenyl or 4-I-phenyl).

30 J. Med. Chem. 1987, 30, 494; and Eur. J. Med. Chem. Chim Ther. 1984, 19,
451, disclose cyclic amines similar to the general Formula III if "n" was 2 and "X"
was NH₂.

SUMMARY OF THE INVENTION

35 In one aspect the subject invention is directed toward compounds and
pharmaceutically acceptable salts of Formula I:



where X and Y are at the 5, 6, or 7 position in place of hydrogen (i.e. replace the hydrogen of a CH) such that:

- 10 i) when n is 1 then X can be $(\text{CH}_2)_m \text{CONR}_4 \text{R}_5$ (where m is 0 or 1), $(\text{CH}_2)_m \text{SO}_2 \text{NR}_4 \text{R}_5$, $(\text{CH}_2)_m \text{NR}_4 \text{CONHR}_5$, $(\text{CH}_2)_m \text{NHSO}_2 \text{R}_3$, $(\text{CH}_2)_m \text{NHCOR}_3$, $\text{C}(\text{O})\text{R}_4$ or $(\text{CH}_2)_m \text{SO}_2 \text{R}_3$ (where for $(\text{CH}_2)_m \text{SO}_2 \text{R}_3$, Y is not hydrogen or halogen); and Y is R_4 , $(\text{CH}_2)_p \text{CONR}_4 \text{R}_5$ (where p is 0 or 1), $(\text{CH}_2)_p \text{CN}$,
15 $(\text{CH}_2)_p \text{SO}_2 \text{NR}_4 \text{R}_5$, OR_6 , $(\text{CH}_2)_p \text{SO}_2 \text{R}_3$, $(\text{CH}_2)_p \text{NHSO}_2 \text{R}_3$, halogen, or $(\text{CH}_2)_p \text{NHCOR}_3$; or
- ii) when n is 0 or 1 then X and Y can be in *ortho*-positions relative to each other and are jointly:
- an N- R_{10} substituted imide such as $-\text{C}(\text{O})\text{NR}_{10}\text{C}(\text{O})-$,
20 $-\text{C}(\text{O})\text{NR}_4(\text{CH}_2)_x \text{NR}_{10}\text{C}(\text{O})-$ (where x is 0 or 1)
- a lactam such as $-\text{CH}_2 \text{NR}_{10}\text{C}(\text{O})-$,
 $-(\text{CH}_2)_2 \text{NR}_{10}\text{C}(\text{O})-$
 $-\text{CH}_2 \text{C}(\text{O})\text{NR}_{10}-$,
 $-\text{N}(\text{R}_3)-\text{C}(\text{O})-\text{N}(\text{R}_3)-$,
25 $-\text{N}(\text{R}_3)-\text{C}(\text{O})-\text{O}-$,
 $-\text{N}=\text{C}(\text{R}_7)-\text{N}(\text{R}_3)-$, or
- a cyclic amine such as $-\text{CH}_2 \text{N}(\text{R}_8)\text{CH}_2-$;
- iii) when n is 0 and Y is OR_9 then X can be $(\text{CH}_2)_m \text{CONR}_4 \text{R}_5$ (where m is 0 or 1), $(\text{CH}_2)_m \text{SO}_2 \text{NR}_4 \text{R}_5$, $(\text{CH}_2)_m \text{NR}_4 \text{CONHR}_5$, $(\text{CH}_2)_m \text{SO}_2 \text{R}_3$,
30 $(\text{CH}_2)_m \text{NHSO}_2 \text{R}_3$, $(\text{CH}_2)_m \text{NHCOR}_3$ or $\text{C}(\text{O})\text{R}_4$;
- R_1 and R_2 are independently H, $\text{C}_1 - \text{C}_8$ alkyl including isomeric forms thereof, or $\text{C}_1 - \text{C}_8$ alkylAryl;
- R_3 is $\text{C}_1 - \text{C}_8$ alkyl, $\text{C}_1 - \text{C}_6$ alkylAryl or Aryl;
- R_4 and R_5 are independently H, $\text{C}_1 - \text{C}_8$ alkyl, $\text{C}_1 - \text{C}_6$ alkylAryl or Aryl;
- 35 R_6 is H, $\text{SO}_2 \text{CF}_3$, $\text{SO}_2 \text{C}_1 - \text{C}_8$ alkyl, $\text{SO}_2 - \text{C}_1 - \text{C}_6$ alkylAryl, $\text{SO}_2 \text{Aryl}$, $\text{C}_1 - \text{C}_8$ alkyl,

$C_1 - C_6$ alkylAryl or Aryl

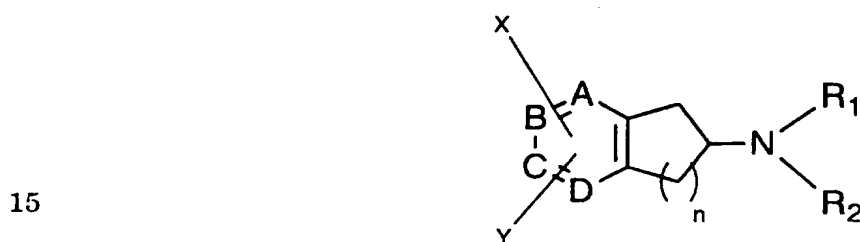
R_7 is hydrogen, $CON(R_4)_2$, $SO_2N(R_4)_2$ or SO_2R_4 ;

R_8 is $C_1 - C_8$ alkyl, $C_1 - C_6$ alkylAryl, Aryl, $CON(R_4)_2$, COR_4 , $SO_2N(R_4)_2$ or SO_2R_4 (provided for $CON(R_4)_2$, COR_4 , $SO_2N(R_4)_2$ or SO_2R_4 , R_4 is not hydrogen);

5 R_9 is $C_2 - C_8$ alkyl (optionally substituted with 1 to 3 halogens), $C_1 - C_6$ alkylAryl, Aryl; and

R_{10} is H, $C_1 - C_8$ alkyl, $C_1 - C_6$ alkylAryl, Aryl or $(CH_2)_{0-6}SO_2Aryl$.

10 In another aspect the subject invention is directed toward compounds and pharmaceutically acceptable salts of Formula II:



wherein one of A, B, C or D is nitrogen and the remaining positions are CH and n is 1 or 2;

20 R_1 and R_2 are independently H, $C_1 - C_8$ alkyl and isomeric forms thereof, $C_1 - C_8$ alkylAryl;

X and Y can be substituted at positions A, B, C, or D in place of hydrogen (i.e. replace the hydrogen of a CH) wherein

- 25 i) X is $(CH_2)_mCONR_4R_5$, $(CH_2)_mCN$, $(CH_2)_mSO_2NR_4R_5$, $(CH_2)_mNR_4CONHR_5$, $(CH_2)_mSO_2R_3$, $(CH_2)_mNHSO_2R_3$, $(CH_2)_mNHCOR_3$ or $C(O)R_4$ (where m is 0 or 1, except that where m is 0, Y is not hydrogen or halogen); and
 Y is R_4 , $(CH_2)_pCONR_4R_5$, $(CH_2)_pCN$, $(CH_2)_pSO_2NR_4R_5$, OR_6 , OSO_2R_3 , $(CH_2)_pSO_2R_3$, $(CH_2)_pNHSO_2R_3$, halogen or $(CH_2)_pNHCOR_3$ (where p is 0 or 1); or
 30 ii) X and Y when in *ortho*-positions relative to each other jointly are
 an N- R_4 substituted imide such as $-C(O)NR_4C(O)-$,
 a lactam such as $-CH_2NR_4C(O)-$ or $-CH_2C(O)NR_4-$
 or a cyclic amine such as $-CH_2NR_4CH_2-$;

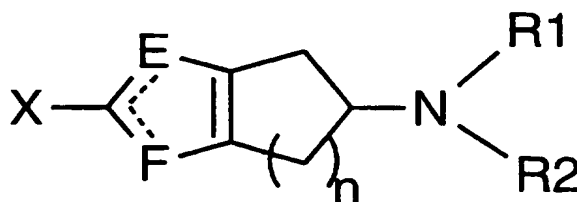
35 R_3 is $C_1 - C_8$ alkyl, $C_1 - C_6$ alkylAryl or Aryl;

R_4 and R_5 are independently H, $C_1 - C_8$ alkyl, $C_1 - C_6$ alkylAryl or Aryl;

and

R_6 is H, SO_2CF_3 , SO_2CH_3 , SO_2Aryl , $\text{C}_1 - \text{C}_8\text{alkyl}$, $\text{C}_1 - \text{C}_6\text{alkylAryl}$ or Aryl .

In another aspect the subject invention is directed toward compounds and
5 pharmaceutically acceptable salts of Formula III:



10

wherein one of E or F is N and the other is S and n is 1 or 2;

R_1 and R_2 are independently H, $\text{C}_1 - \text{C}_8$ alkyl and isomeric forms thereof or
 $\text{C}_1 - \text{C}_8$ alkylAryl;

where X is $(\text{CH}_2)_m\text{CONR}_4\text{R}_5$, $(\text{CH}_2)_m\text{CN}$, $(\text{CH}_2)_m\text{SO}_2\text{NR}_4\text{R}_5$,
15 $\text{CH}_2\text{NR}_4\text{CONHR}_5$, $(\text{CH}_2)_m\text{SO}_2\text{R}_3$, $(\text{CH}_2)_m\text{NHSO}_2\text{R}_3$ or $\text{CH}_2\text{NHCOR}_3$,
 $\text{C}(\text{O})\text{R}_4$;

R_3 is $\text{C}_1 - \text{C}_8$ alkyl, $\text{C}_1 - \text{C}_6$ alkylAryl or Aryl;

R_4 and R_5 are independently H, $\text{C}_1 - \text{C}_8$ alkyl, $\text{C}_1 - \text{C}_6$ alkylAryl or Aryl;

and where m is 0 or 1.

20

In another aspect the subject invention is directed toward compounds and
pharmaceutically acceptable salts of Formula I, II or III, above, including racemic
mixtures and as both enantiomers.

In yet another aspect the subject invention is a method for treating
25 schizophrenia by administering a therapeutically effective amount of a compound of
Formula I, II or III to a patient suffering from schizophrenia. The compounds of
Formula I, II or III can be administered to a patient suffering from schizophrenia,
mania, depression, geriatric disorders, drug abuse and addiction, Parkinson's
disease, sleep disorders, circadian rhythm disorders, anxiety disorders or dementia.
30 The compounds can be administered in an amount of from about 0.25 mg to about
100 mg/person.

In yet another aspect, the subject invention is directed toward a method for
treating central nervous system disorders associated with the dopamine D3 receptor
activity in a patient in need of such treatment comprising administering to the
35 subject a therapeutically effective amount of a Formula I, II or III compound for
alleviation of such disorder. Typically, the compound of Formula I, II or III is

administered in the form of a pharmaceutical composition comprising a pharmaceutically-acceptable carrier or diluent.

In yet another aspect, the subject invention is directed toward a pharmaceutical composition for treating central nervous system disorders associated with the dopamine D3 receptor activity comprising an effective amount of a
5 compound of Formula I, II or III with a pharmaceutically-acceptable carrier or diluent.

DETAILED DESCRIPTION OF THE INVENTION

10 The subject invention is directed toward compounds or pharmaceutically acceptable salts of Formula I, II or III as depicted above in either racemic or pure enantiomer forms.

"Alkyl" are one to eight or six carbon atoms such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl and isomeric forms thereof.

15 "Halogen" is an atom of fluorine, chlorine, bromine or iodine.

"Aryl" includes phenyl, pyridinyl, imidazolyl, thiophenyl, oxazolyl, oxadiazole, benzotriazole, benzooxadiazole, thiazole, and isoxazolyl. Aryl can be substituted with one or more fluorine, chlorine, bromine, amino, CN, carboxamido, acetamido, methyl, nitro, sulfonyl, sulfonamido, trifluoromethyl, thifluoromethoxy, O-alkoxy,
20 triflate, or acetyl.

Pharmaceutically acceptable salts include salts of both inorganic and organic acids. The preferred pharmaceutically acceptable salts include salts of the following acids: methanesulfonic, hydrochloric, hydrobromic, sulfuric, phosphoric, nitric, benzoic, citric, tartaric, fumaric or maleic.

25 The compounds of Formula I, II or III are active orally or parenterally. Orally the Formula I, II or III compounds can be given in solid dosage forms such as tablets or capsules, or can be given in liquid dosage forms such as elixirs, syrups or suspensions as is known to those skilled in the art. It is preferred that the Formula I, II or III compounds be given in solid dosage form and that it be a tablet.

30 Typically, the compounds of Formula I, II or III can be given in the amount of about 0.5 mg to about 250 mg/person, one to three times a day. Preferably, about 5 to about 50 mg/day in divided doses.

The exact dosage and frequency of administration depends on the particular compound of Formula I, II or III used, the particular condition being treated, the
35 severity of the condition being treated, the age, weight, general physical condition of the particular patient, other medication the individual may be taking as is well

known to those skilled in the art and can be more accurately determined by measuring the blood level or concentration of the active compound in the patient's blood and/or the patient's response to the particular condition being treated.

Thus, the subject compounds, along with a pharmaceutically-acceptable carrier, diluent or buffer, can be administered in a therapeutic or pharmacological amount effective to alleviate the central nervous system disorder with respect to the physiological condition diagnosed. The compounds can be administered intravenously, intramuscularly, topically, transdermally such as by skin patches, buccally or orally to man or other vertebrates.

The compositions of the present invention can be presented for administration to humans and other vertebrates in unit dosage forms, such as tablets, capsules, pills, powders, granules, sterile parenteral solutions or suspensions, oral solutions or suspensions, oil in water and water in oil emulsions containing suitable quantities of the compound, suppositories and in fluid suspensions or solutions.

For oral administration, either solid or fluid unit dosage forms can be prepared. For preparing solid compositions such as tablets, the compound can be mixed with conventional ingredients such as talc, magnesium stearate, dicalcium phosphate, magnesium aluminum silicate, calcium sulfate, starch, lactose, acacia, methylcellulose, and functionally similar pharmaceutical diluent or carrier materials. Capsules are prepared by mixing the compound with an inert pharmaceutical diluent and filling the mixture into a hard gelatin capsule of appropriate size. Soft gelatin capsules are prepared by machine encapsulation of a slurry of the compound with an acceptable vegetable oil, light liquid petrolatum or other inert oil.

Fluid unit dosage forms for oral administration such as syrups, elixirs, and suspensions can be prepared. The forms can be dissolved in an aqueous vehicle together with sugar, aromatic flavoring agents and preservatives to form a syrup. Suspensions can be prepared with an aqueous vehicle with the aid of a suspending agent such as acacia, tragacanth, methylcellulose and the like.

For parenteral administration, fluid unit dosage forms can be prepared utilizing the compound and a sterile vehicle. In preparing solutions, the compound can be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampoule and sealing. Adjuvants such as a local anesthetic, preservative and buffering agents can be dissolved in the vehicle. The composition can be frozen after filling into a vial and the water removed under vacuum. The lyophilized powder can then be sealed in the vial and reconstituted prior to use.

Binding Data for Examples:

Competition binding experiments employed eleven dilutions of test compounds of Formula I competing with [³H]-5-(dipropylamino)-5,6-dihydro-4H-imidazo(4,5,1-ij)quinolin-2(1H)-one (R-enantiomer) ("86170") (62 Ci/mmol, 2nM) and [³H]-spiperone ("SPI") (107 Ci/mmol, 0.5 nM) for D2 and D3 binding sites, respectively. (Lahti, R.A., Eur. J. Pharmacol., 202, 289 (1991)) In each experiment, cloned rat receptors expressed in CHO-K1 cells were used. (Chio, C.L., Nature, 343, 266 (1990); and Huff, R.M., Mol. Pharmacol. 45, 51-60 (1993)). The results are shown in Table I.

TABLE I

	<u>Example #</u>	<u>Receptor</u>	<u>Ligand</u>	<u>Ki (nM)</u>
15	2	D2-DOP-CLONE	86170	1436
		D3-DOP-CLONE	SPI	32
	3	D2-DOP-CLONE	86170	206
		D3-DOP-CLONE	SPI	12
	4	D2-DOP-CLONE	86170	772
		D3-DOP-CLONE	SPI	109
20	5	D2-DOP-CLONE	86170	786
		D3-DOP-CLONE	SPI	*
	6	D2-DOP-CLONE	86170	1684
		D3-DOP-CLONE	SPI	1453
	8	D2-DOP-CLONE	86170	177
		D3-DOP-CLONE	SPI	87
25	9	D2-DOP-CLONE	86170	*
		D3-DOP-CLONE	SPI	*
	10	D2-DOP-CLONE	86170	324
		D3-DOP-CLONE	SPI	18
	11	D2-DOP-CLONE	86170	>2235
		D3-DOP-CLONE	SPI	195

30 * indicates compound was inactive.

Legend of Examples: Formula I wherein n is 1, R₁ and R₂ are n-propyl, Y is H and X is substituted at the 7 position as follows:

<u>Ex. #</u>	<u>X</u>	<u>Ex#</u>	<u>X</u>	
35	2	CH ₂ NHSO ₂ -4-CN-phenyl	3	CH ₂ NHSO ₂ -4-Cl-phenyl
	4	CH ₂ NHSO ₂ -4-NO ₂ -phenyl	5	CH ₂ NHSO ₂ -3-CN-phenyl
	6	CH ₂ NHSO ₂ -4-methyl-imidazole	8	CH ₂ NHC(O)-4-Cl-phenyl
	9	CH ₂ NHC(O)-4-CN-phenyl	10	NHSO ₂ -4-Cl-phenyl
	11	NHSO ₂ -4-CN-phenyl		

As was done for Table I, competition binding experiments employed eleven dilutions of test compounds of Formula II competing with [^3H]-5-(dipropylamino)-5,6-dihydro-4H-imidazo(4,5,1-ij)quinolin-2(1H)-one (R-enantiomer) ("**86170**") (62 Ci/mmol, 2nM) and [^3H]-7-OH-DPAT ("**7-OH-DPAT**") (107 Ci/mmol, 0.5 nM) for D2 and D3 binding sites, respectively. (Lahti, R.A., Eur. J. Pharmacol., 202, 289 (1991)) In each experiment, cloned rat receptors expressed in CHO-K1 cells were used. (Chio, C.L., Nature, 343, 266 (1990); and Huff, R.M., Mol. Pharmacol., 45, 51-60 (1993). K_i values were calculated with the Chen-Prushoff equation. The results are shown in Table II for compounds prepared under Scheme 5.

10

TABLE II

COMPOUND #	Receptor	Ligand	K_i (nM)
52	D2-DOP-CLONE	86170	357
	D3-DOP-CLONE	7-OH-DPAT	6
53	D2-DOP-CLONE	86170	184
15	D3-DOP-CLONE	7-OH-DPAT	3

Chemical Synthesis:

Scheme 1 and Scheme 2: (Formula I analogs)

The N-carbomethoxy anhydride prepared from D-aspartic acid (**1**, Scheme 1) underwent an aluminum chloride mediated Friedel-Crafts reaction with bromobenzene to afford ketone **2**. This ketone underwent reduction of the ketone group with triethylsilane catalyzed by titanium tetrachloride, to give **3**. This carboxylic acid was converted to the acid chloride which then underwent an aluminum chloride catalyzed Friedel-Crafts cyclization to obtain tetralone **4**. This ketone was reduced with triethylsilane, catalyzed by titanium tetrachloride, to give tetralin **5**. The carbamate group was saponified with hydroxide to give 7-bromo-2-aminotetralin **6**, which was then alkylated to give **7**. Treatment of this aryl bromide with t-butyllithium followed by trimethylsilylisocyanate (*Tetrahed. Lett.* **1975**, 981), followed by aqueous hydrolysis, gave carboxamide **8**. Refluxing this carboxamide in THF with borane resulted in reduction to primary amine **9**. This amine (**9**) was treated with various sulfonyl chlorides (**Procedure 9**) to obtain sulfonamides **10** - **15**.

Sulfonamide **11** was further transformed to **16** (Scheme 2) by hydrolysis of the nitrile with hydrogen peroxide to obtain carboxamide **16** (*Tetrahed. Lett.* **1989**,

949).

Primary amine **9** was also converted into carboxamides **17** and **18** using the appropriate carboxylic acid chloride (Scheme 2).

Aryl bromide **7** was treated with *t*-butyllithium, followed by
5 diphenylphosphorylazide, and then by sodium bis(2-methoxyethoxy)aluminum hydride (Scheme 2) to afford amine **19** (*Tetrahed. Lett.* **1984**, 429). This amine was treated with sulfonyl chlorides to obtain sulfonamides **20** and **21**.

Scheme 3 :(Formula I analogs)

10 Aminotetralin **22** (*J. Org. Chem.* **1995**, 4324) was protected with a BOC-group and then subjected to metal-halogen exchange with *t*-butyllithium, followed by DMF quench to obtain an aldehyde. This aldehyde was reduced with sodium borohydride to obtain a benzylic alcohol. This was treated with thionyl chloride to obtain the
15 benzylic chloride, which in turn was converted into the benzylic azide with sodium azide. Pd/C catalyzed hydrogenation of the azide afforded benzylic amine **24**. This amine was condensed with various aryl sulfonyl chlorides to obtain the sulfonamides. These were treated with trifluoroacetic acid to remove the BOC-protecting groups (**procedure 16**), affording sulfonamide compounds **25** - **26**. These were alkylated with bromopropane (**procedure 17**) to obtain the tertiary amine
20 sulfonamides represented by **27**.

Amine **24** was also condensed with aryl carboxylic acid chlorides to generate amides, which were then deprotected with trifluoroacetic acid to obtain amides **28** - **29**. These amides (**28** - **29**) were heated with bromopropane (**procedure 17**) to generate the tertiary amine analogs, represented by **30**.

25 Amine **24** was also condensed with aryl isocyanates to obtain ureas. These were deprotected with trifluoroacetic acid to generate ureas **31** - **33**.

Scheme 4: (Formula I analogs)

Diyne acid **34** (*J. Chem. Soc., Perkin Trans. I*, 1215-1224 (1986)) was induced
30 to undergo a Curtius rearrangement with diphenylphosphoryl azide, trapping the isocyanate intermediate with *t*-butanol to obtain the BOC-protected product. The BOC-group was cleaved with trifluoroacetic acid to afford the primary amine, which was then treated with trifluoroacetic anhydride to obtain **35**. This diyne (**35**) was treated with Wilkinson's catalyst and the 1,4-diacetoxy-2-butyne to afford **36**
35 (*Tetrahed. Lett.*, **34**, 23-26 (1993)). The acetates and trifluoroacetyl group were

cleaved with base and the product alkylated with n-bromopropane to afford **37**. This diol was treated with allylamine to give the 5-membered amine ring; subsequently the allyl group was removed with palladium catalysis to afford **38**. Amine **38** was condensed with various arylsulfonyl chlorides (**procedure 9**) to afford sulfonamides **39 - 46**.

Scheme 5 : (Formula II analogs)

Pyridone **47** (*J. Chem. Soc. Perkin Trans. 1990*, 195) was hydrolyzed (Scheme 5) with aqueous perchloric acid at 95°C to obtain ketone **48**. This ketone underwent reductive amination with n-propylamine using 50 p.s.i. hydrogenation gas and acetic acid and platinum oxide in ethanol. The propyl-substituted amine (**49**) was obtained in good yield. Treatment with di-*t*-butyl dicarbonate in THF afforded the BOC-protected compound (**50**). This was condensed with 4-chlorobenzenesulfonyl chloride in the presence of DMAP and triethylamine to give sulfonyloxy substituted pyridine **51**. Deprotection of the BOC group with trifluoroacetic acid at 25°C gave amine **52** after workup. This could be converted to the dipropylamine analog (**53**) by heating with n-bromopropane in acetonitrile in the presence of potassium carbonate.

Scheme 6 : (Formula II analogs)

Diyne **54**, whose preparation is already described, was treated with N-benzyloxy-2-aminoacetone under the influence of cobalt catalysis (*J. Chem. Soc., Chem. Comm.*, 133-134 (1982)) to obtain heterocycle **55**. The BOC-group was removed with trifluoroacetic acid and the amine was alkylated with n-bromopropane to afford **56**. The CBZ-group was removed by palladium catalyzed hydrogenation to afford amine **57**. This amine was treated with aryl sulfonyl chlorides (**procedure 9**) to obtain sulfonamides represented by **58 - 59**.

Amine **57** was also treated with arylcarboxylic acid chlorides (**procedure 11**) to obtain amides represented by **60**.

Amine **57** was also treated with aryl isocyanates (**procedure 33**) to obtain ureas represented by **61 - 62**.

Scheme 7: (Formula III analogs)

Ketone **63** (*Helv. Chim. Acta 1994* 1256) underwent reductive amination with sodium cyanoborohydride in the presence of acetic acid and propanal to afford **64**. This amine was protected with a BOC-group and the compound was treated with n-

butyllithium at low temperature followed by a quench with dimethylformamide to afford aldehyde **65**. This aldehyde was condensed with hydroxylamine hydrochloride to obtain **66**. Oxime **66** was reduced with Devarda's alloy (alloy of 50% copper, 45% aluminum, 5% zinc) to obtain amine **67**. This amine was treated with 4-chlorophenylisocyanate to obtain urea **68**.

Scheme 8: (Formula I analogs)

The hydroxy, triflate **69** (Patent 4714) was alkylated with various alkyl halides using sodium hydride in DMF to afford the intermediates **70-73** (**procedure 38**). These triflate intermediates were converted via carbonylation using palladium acetate and 1,3-bis(diphenylphosphinopropane) under carbon monoxide atmosphere (**procedure 39**) to yield the methyl ester intermediates **74-77**. These methyl ester intermediates were converted to either the primary carboxamide products **78-81** using formamide and sodium methoxide (**procedure 40**) or converted to the alkylcarboxamide products **82-84** using appropriate substituted formamides and sodium methoxide (**procedure 41**). The primary carboxamide **81** was further elaborated using sodium hydride and an alkyl halide (**procedure 42**) to the alkylcarboxamide product **85**.

The hydroxy, ester **86** (patent 4714) was converted to the carboxamide **87** using sodium methoxide and formamide (**procedure 43**) followed by alkylation using potassium carbonate and alkyl halides (**procedure 44**) to give **88-90**.

Scheme 9: (Formula I analogs)

The dimethylester **91** (patent 4714) was hydrolyzed to the dicarboxylic acid **92** using aqueous NaOH/MeOH (**procedure 45**). This diacid was then condensed and cyclized with ammonium acetate and HCl in acetic acid to give **93** (**procedure 46**) or alternatively condensed with various amines in acetic acid to give **95-124** (**procedure 49**). The products **93, 95-124** were reduced to the corresponding lactam derivatives **94, 125-133** with zinc/acetic acid (**procedure 47**). The intermediates **93** and **94** were also alkylated with various substituted halides to give **95-124** and **125-133** (**procedure 48** and **50**).

Scheme 10: (Formula I analogs)

The dicarboxylic acid **92** was condensed with various hydrazines in acetic acid to give **134-135** (pr cedure **51**).

5

The following procedures 1-9 from Scheme 1 are useful in the preparation of the Examples 1-6 of this invention (with the exception of Example 5 which was inactive in the dopamine screen).

10

Procedure 1:(R)-4-Bromo- α -[(methoxycarbonyl)amino]- γ -oxobenzenebutanoic acid. 2

A mixture of bromobenzene (373 g) and (R)-2-carbomethoxyaminosuccinic anhydride (**1**) (90.51 g) in dichloromethane (260 ml) was cooled in ice, and aluminum chloride (174.34 g) was added over 1 minute (exothermic!). The dark red mixture was stirred at 0°C for 30 minutes and at room temperature for 1 hour. The mixture was poured onto crushed ice, and concentrated hydrochloric acid was added slowly with stirring. Diethylether was added and the mixture was stirred until all of the red-brown material disappeared. The layers were separated, and the aqueous was extracted twice more with diethylether. The combined ether extracts were washed with water and extracted with aqueous sodium carbonate. The combined extracts were washed with diethylether, cooled in ice, and acidified with conc. hydrochloric acid. The acid was extracted 3 times with diethylether. The combined extracts were washed with brine and dried (MgSO₄). The solvent was removed under vacuum to leave the title compound as a foam, 149.6 g. $[\alpha]_D = -41^\circ$ (25°C, CH₃OH, c = 1.0352).

20

25

Procedure 2: (R)-4-Bromo- α -[(methoxycarbonyl)amino]benzenebutanoic acid. 3

A solution of (R)-4-bromo- α -[(methoxycarbonyl)amino]- γ -oxobenzenebutanoic acid (**2**) (74.35 g) in dichloromethane and triethylsilane (182 ml) was cooled to 0°C and titanium tetrachloride (99.0 ml) was added dropwise over a period of 15 minutes with stirring. After 5.5 hours, triethylsilane (72 ml) was added, and the mixture was stirred at room temperature for 17 hours and at reflux on the steam bath for 3 hours. The mixture was cooled and poured onto ice. The mixture was extracted twice with diethylether. The combined ether extracts were washed with water and extracted 3 times with 250 ml portions of 10% sodium carbonate solution. The combined extracts were washed with diethylether, cooled in ice, and acidified with

30

35

concentrated hydrochloric acid. The precipitate was filtered, washed with water, and dried under vacuum to leave a white solid. Crystallization from ethyl acetate/hexane gave the title compound as white crystals (52.7 g, 74%, m.p. 136-137°C). $[\alpha]_D = -12^\circ$ (25°C, CH₃OH, c = 0.8709).

5 **Procedure 3: Methyl (R)-(7-Bromo-1,2,3,4-tetrahydro-1-oxo-2-naphthalenyl)carbamate. 4**

A suspension of (R)-4-bromo- α -[(methoxycarbonyl)amino]benzenebutanoic acid (3) (97.0 g) in dichloromethane was cooled in ice, and dimethyl formamide (1.2 ml) and oxalyl chloride (28.1 ml) were added. The mixture was stirred at 0°C for 5
10 minutes and at room temperature for 1.5 hours. The solution was cooled to -25°C, and aluminum chloride (86.4 g) was added portionwise over 12 minutes. The mixture was stirred at -20°C for 40 minutes and poured onto a mixture of ice, 10% hydrochloric acid (300 ml), and chloroform (100 ml) with stirring. The mixture was extracted twice with diethylether, and the extracts were washed with water,
15 saturated sodium bicarbonate solution, and brine. The solution was dried (MgSO₄), and the solvent was removed under vacuum to leave a slightly yellow solid (91.76 g). Crystallization from methanol gave colorless crystals which were filtered, washed with hexane and dried under vacuum (69.9 g, 76% m.p. 116-117°C). The filtrate was evaporated and the residue was recrystallized from methanol to give more of the
20 title compound as an off-white solid (6.81 g, m.p. 111-112°C). $[\alpha]_D = +43^\circ$ (25°C, CH₃OH, c = 0.8143).

Procedure 4: Methyl (R)-(7-Bromo-1,2,3,4-tetrahydro-2-naphthalenyl)carbamate. 5

Into a 2-l, 3-necked flask equipped with a mechanical stirrer, a 125 ml
25 addition funnel, and a N₂ inlet was placed a solution of methyl (R)-(7-bromo-1,2,3,4-tetrahydro-1-oxo-2-naphthalenyl)carbamate (4) (68.74 g) in dichloromethane. Triethylsilane (147 ml) was added, and the mixture was cooled in ice. Titanium tetrachloride (76.2 ml) was added via the addition funnel over a period of 10 minutes, and the mixture was stirred at room temperature for 24 hours.
30 Triethylsilane (18.5 ml) was added, and the mixture was stirred for an additional 2 hours. The mixture was poured onto ice, the layers were separated, and the aqueous layer was extracted twice with dichloromethane. The combined extracts were washed twice with 5% hydrochloric acid, once with water, and once with 5% sodium hydroxide solution. The solution was dried (MgSO₄), and the solvent was
35 removed under vacuum to leave an oil which partially crystallized (122.9 g). The mixture was diluted with hexane, cooled in ice, and filtered giving a white solid

(60.88 g). Crystallization from ethyl acetate/hexane gave the title compound as colorless crystals (52.69 g, 0.185 mol, 80.3%, m.p. 99-100.5°C). A second crop (5.29 g) was obtained. Chiral HPLC analysis: (Chiralcel OD column, Daicel Chem. Ind., LTD; 10% isopropanol in hexane; 1 ml/min flow rate; $\lambda = 215$; 25 cm x 4.6 mm id column) shows 3.26 min (1.5%), 8.57 min (1.7%), 10.66 min (96.9%), 13.97 min (1.6%). The racemate shows 3.27 min (1.2%), 8.66 min (0.3%), 10.75 min (48.9%), 14.30 min (49.4%), 25.79 min (0.2%). $[\alpha]_D = +74^\circ$ (25°C, CH₃OH, c = 0.8884).

Procedure 5: (R)-7-Bromo-1,2,3,4-tetrahydro-2-naphthalenamine (Z)-2-butenedioate (1:1). 6

Methyl (R)-(7-bromo-1,2,3,4-tetrahydro-2-naphthalenyl)carbamate (5) (51.62 g), potassium hydroxide (61.2 g), water (150 ml) and ethanol (350 ml) were heated at reflux for two days. The ethanol was removed under vacuum, and the residue was partitioned between water and 2:1 diethylether/tetrahydrofuran. The aqueous layer was extracted again with the same solvent, and the combined extracts were washed with brine and dried (MgSO₄). The solvent was removed under vacuum to leave an oil (37.9 g). A sample of the compound (15.28 g) was combined with maleic acid (7.85 g), and the mixture was crystallized from methanol/diethylether to give the title compound as colorless crystals (19.24 g, m.p. 184-184.5°C). $[\alpha]_D = +40^\circ$ (25°C, CH₃OH, c = 0.7756). A second crop (2.05 g) was obtained.

Procedure 6: (R)-7-Bromo-1,2,3,4-tetrahydro-N,N-dipropyl-2-naphthalenamine 4-Methylbenzenesulfonate. 7

A mixture of (R)-2-amino-3-bromo-1,2,3,4-tetrahydronaphthalene (6) (22.62 g), 1-bromopropane (36.4 ml), and potassium carbonate (41.5 g) in acetonitrile was stirred at reflux for 16 hours. 1-Bromopropane (20 ml) was added, and the reflux was continued for 8 hours. The mixture was partitioned between water and diethylether. The aqueous layer was extracted again with diethylether, and the combined ether extracts were washed with brine and dried (MgSO₄). The solvent was removed under vacuum to leave an oil (29.18 g). Purification by flash chromatography (230-400 mesh silica gel, ethyl acetate/hexane) gave an oil (26.4 g, 85%). A sample (0.997 g) was combined with p-toluenesulfonic acid hydrate (0.62 g), and crystallized from methanol/diethylether to give the title compound as colorless crystals (1.39 g, m.p. 182-183.5°C). $[\alpha]_D = +48^\circ$ (25°C, CH₃OH, c = 0.9834).

Procedure 7: (R)-7-(Dipropylamino)-5,6,7,8-tetrahydro-2-naphthal ncarboxamide. 8

A solution of (R)-2-(dipropylamino)-7-bromo-1,2,3,4-tetrahydronaphthalene (7) (13.02 g) in dry tetrahydrofuran was cooled to -78°C. t-Butyllithium (1.7 M in

pentane, 50.6 ml) was added via syringe over a period of 6 minutes, and the mixture was stirred for an additional 8 minutes. Trimethylsilylisocyanate (13.4 ml, 85% pure, 84.1 mmol) was added in one dose, and the mixture stirred at -78°C for 10 minutes and at room temperature for 1.5 hours. The reaction mixture was quenched
5 with 10% hydrochloric acid, and after stirring for 30 minutes, it was basified with 15% sodium hydroxide. The free base was extracted with diethylether and 1:1 tetrahydrofuran/diethylether. The combined extracts were washed with brine and dried (MgSO₄). The solvent was removed under vacuum to leave an oil (15.25 g). Crystallization from ethyl acetate/hexane gave off-white crystals (6.30 g), m.p. 132-
10 132°C. $[\alpha]_D = +67^\circ$ (25°C, CH₃OH, c = 0.8139).

Procedure 8: (R)-7-(Dipropylamino)-5,6,7,8-tetrahydro-2-naphthalenemethanamine. 9

A solution of the (R)-7-(dipropylamino)-5,6,7,8-tetrahydro-2-naphthalenecarboxamide (8) (8.68 g) in dry tetrahydrofuran was stirred at room
15 temperature and borane dimethylsulfide complex (10.0 M, 11.1 ml) was slowly added. When the initial reaction subsided, the mixture was heated at reflux for 2 days. The mixture was cooled in ice, and water was added dropwise. When the evolution of gas ceased, 10% hydrochloric acid (75 ml) was added, and the mixture was refluxed for 2 hours. The mixture was cooled in ice and basified with solid
20 sodium hydroxide. The mixture was extracted with diethylether and then with 2:1 diethylether/tetrahydrofuran. The combined extracts were washed with brine and dried (MgSO₄). The solvent was removed under vacuum to leave the title compound a yellow oil (8.15 g) which was used without further purification.

EXAMPLE 1: Procedure 9: (R)-N-[[7-(Dipropylamino)-5,6,7,8-tetrahydro-2-naphthalenyl]methyl]methanesulfonamide. 10

A solution of crude (R)-7-(dipropylamino)-5,6,7,8-tetrahydro-2-naphthalenemethanamine (9) (0.521 g) and triethylamine (0.30 ml) in tetrahydrofuran was cooled to 0°C. Methanesulfonyl chloride (0.16 ml) was added dropwise with stirring. The mixture was stirred at room temperature for 1.5 hours
30 and quenched with 10% sodium carbonate solution. The mixture was extracted twice with diethylether and the combined extracts were washed with brine and dried (MgSO₄). The solvent was removed under vacuum to leave an oil (0.63 g). Purification by flash chromatography (ethyl acetate/hexane) gave the title compound as a colorless oil (0.47 g). $[\alpha]_D = +58^\circ$ (25°C, CH₃OH, c = 0.5221).

EXAMPLE 2: (R)-4-Cyano-N-[[7-(dipropylamino)-5,6,7,8-tetrahydro-2-naphthalenyl]methyl]benzenesulfonamide. 11

Using procedure 9, a solution of crude (R)-7-(dipropylamino)-5,6,7,8-tetrahydro-2-naphthalenemethanamine (9) was treated with 4-cyanophenylsulfonyl chloride. Purification by chromatography gave a sample which was crystallized from ethyl acetate/hexane to give 11 as colorless crystals (m.p. 94-95.5°C). $[\alpha]_D = +46^\circ$ (25°C, CH₃OH, c = 0.7967).

EXAMPLE 3: (R)-4-Chloro-N-[[7-(dipropylamino)-5,6,7,8-tetrahydro-2-naphthalenyl]methyl]benzenesulfonamide. 12

Using procedure 9, (R)-7-(dipropylamino)-5,6,7,8-tetrahydro-2-naphthalenemethanamine (9) was treated with 4-chlorobenzenesulfonyl chloride. Purification by chromatography gave a solid which was crystallized from hexane to give the title compound colorless crystals (m.p. 72°C). $[\alpha]_D = +47^\circ$ (25°C, CH₃OH, c = 0.6095).

EXAMPLE 4: (R)-4-Nitro-N-[[7-(dipropylamino)-5,6,7,8-tetrahydro-2-naphthalenyl]methyl]benzenesulfonamide. 13

Using procedure 9, (R)-7-(dipropylamino)-5,6,7,8-tetrahydro-2-naphthalenemethanamine 9 and triethylamine in dry tetrahydrofuran was cooled to 0°C, and 4-nitrobenzenesulfonyl chloride was added. After extraction, purification by flash chromatography (ethyl acetate/hexane) gave a solid which was crystallized from hexane containing a small amount of ethyl acetate to give 13 as yellow crystals (m.p. 105°C). $[\alpha]_D = +49^\circ$ (25°C, CH₃OH, c = 0.9425).

EXAMPLE 5: (R)-3-Cyano-N-[[7-(dipropylamino)-5,6,7,8-tetrahydro-2-naphthalenyl]methyl]benzenesulfonamide. 14 (Inactive in dopamine screen)

Using procedure 9, (R)-7-(dipropylamino)-5,6,7,8-tetrahydro-2-naphthalenemethanamine 9 and triethylamine in dry tetrahydrofuran was cooled to 0°C, and 3-cyanobenzenesulfonyl chloride was added. After extraction, purification by flash chromatography (ethyl acetate/hexane) gave the title compound as an oil. $[\alpha]_D = +41^\circ$ (25°C, CH₃OH, c = 1.0394).

EXAMPLE 6: (R)-N-[[7-(Dipropylamino)-5,6,7,8-tetrahydro-2-naphthalenyl]methyl]-1-methyl-1H-imidazole-4-sulfonamide. 15

Using procedure 9, (R)-7-(dipropylamino)-5,6,7,8-tetrahydro-

2-naphthalenemethanamine **9** and triethylamine in dry tetrahydrofuran was cooled to 15°C, and 1-methylimidazole-4-sulfonyl chloride was added. After extraction, purification by flash chromatography (tetrahydrofuran/ethyl acetate) gave the title compound as an oil. $[\alpha]_D = +46^\circ$ (25°C, CH₃OH, c = 0.7458).

5

EXAMPLE 7: Procedure 10. (R)-Carboxamido-N-[[7-(dipropylamino)-5,6,7,8-tetrahydro-2-naphthalenyl]methyl]benzenesulfonamide. 16

(R)-4-Cyano-N-[[7-(dipropylamino)-

5,6,7,8-tetrahydro-2-naphthalenyl]methyl]benzenesulfonamide (**11**) was treated with
10 hydrogen peroxide and sodium hydroxide in aqueous THF. After completion of the hydrolysis the solution was extracted with ether/water. The ether layer was dried over sodium sulfate and the solvent removed. The residue was chromatographed with ethyl acetate/hexane to afford **16** as a solid.

15 **EXAMPLE 8: Procedure 11. (R)-4-Chloro-N-[[7-(dipropylamino)-5,6,7,8-tetrahydro-2-naphthalenyl]methyl]benzamide. 17**

(R)-7-(dipropylamino)-5,6,7,8-tetrahydro-2-naphthalenemethanamine **9** (0.521 g) and triethylamine (0.30 ml) in tetrahydrofuran (6 ml) were cooled to 0°C, and 4-chlorobenzoyl chloride (0.254 ml) was added. The mixture was allowed to warm to
20 room temperature and was stirred for 3 hours. The reaction was quenched with 10% sodium carbonate solution, and the mixture was stirred for 30 minutes. The mixture was extracted twice with 1:1 tetrahydrofuran/diethylether, and the combined organics were washed with brine and dried (MgSO₄). The solvent was removed under vacuum to leave a solid which was crystallized from ethyl acetate to
25 give the title compound as colorless crystals (0.52 g, m.p. 209.5°C). $[\alpha]_D = +42^\circ$ (25°C, CHCl₃, c = 0.9118).

EXAMPLE 9: (R)-4-Cyano-N-[[7-(dipropylamino)-5,6,7,8-tetrahydro-2-naphthalenyl]methyl]benzamide. 18 (A comparison example for this
30 invention)

Using procedure 11, (R)-2-(dipropylamino)-7-amino-1,2,3,4-tetrahydronaphthalene **9** and triethylamine in tetrahydrofuran were cooled to 0°C, and 4-cyanobenzoyl chloride was added. After extraction, etc., the solid was crystallized from ethyl acetate to give the title compound as off-white crystals
35 (m.p.183°C). $[\alpha]_D = +50^\circ$ (25°C, CH₃OH, c = 0.9773).

Procedure 12. (R)-2-(Dipropylamino)-7-amino-1,2,3,4-tetrahydronaphthalene. 19

(R)-2-(Dipropylamino)-7-bromo-1,2,3,4-tetrahydronaphthalene **7** (5.91 g) was dissolved in dry tetrahydrofuran (50 ml) under nitrogen and cooled to -78°C. t-Butyllithium (1.7 M in pentane, 23.0 ml) was added over 5 minutes, and the mixture was stirred at -78°C for an additional 10 minutes. This solution was added via needlestock to a solution of diphenylphosphoryl azide (5.24 g) in tetrahydrofuran (30 ml) over a 10 minute period. The mixture was stirred at -78°C for 2 hours and was warmed to -20°C over 45 minutes. The mixture was again cooled to -78°C, and sodium bis(2-methoxyethoxy)aluminum hydride (3.4 M in toluene, 22.4 ml) was added over 5 minutes. After stirring at -78°C for an additional 10 minutes, the mixture was warmed to 0°C and stirred for 45 minutes and at room temperature for 30 minutes. The mixture was carefully quenched with water, and saturated with sodium chloride. The amine was extracted twice with diethylether, and the combined extracts were dried (MgSO₄). The solvent was removed under vacuum to leave an oil (6.3 g). Purification by flash chromatography gave the **19** as a light amber oil (2.56 g).

EXAMPLE 10: Procedure 13. (R)-4-Chloro-N-[7-(dipropylamino)-5,6,7,8-tetrahydro-2-naphthalenyl]benzenesulfonamide 20

p-Chlorobenzenesulfonyl chloride (0.32 g) was added to a solution of (R)-2-(dipropylamino)-7-amino-1,2,3,4-tetrahydronaphthalene **19** (0.370 g) and triethylamine (0.30 ml) in dry tetrahydrofuran (4 ml). The mixture was stirred at room temperature overnight. The reaction was quenched with 10% sodium carbonate solution (5 ml), and the mixture was stirred for 10 minutes. The mixture was extracted twice with diethylether, and the combined extracts were washed with brine and dried (MgSO₄). The solvent was removed under vacuum to leave an oil (0.63 g). Purification by flash chromatography (ethyl acetate in hexane) gave **20** as an amber oil. $[\alpha]_D^{25} = +52^\circ$ (25°C, CH₃OH, c = 1.0535).

EXAMPLE 11: (R)-4-Cyano-N-[7-(dipropylamino)-5,6,7,8-tetrahydro-2-naphthalenyl]benzenesulfonamide. 21

Using procedure 13, p-cyanobenzenesulfonyl chloride was added to a solution of crude (R)-2-(dipropylamino)-7-amino-1,2,3,4-tetrahydronaphthalene **19** and triethylamine in dry tetrahydrofuran. After extraction, etc., purification by flash

chromatography (ethyl acetate in hexane) gave **21** as an amber oil which could be crystallized as its fumarate salt from methanol/ether (m.p. 123°C dec). $[\alpha]_D^{25} = +48^\circ$ (25°C, CH₃OH, c = 1.0113).

5 **Procedure 14: *tert*-Butyl (R)-(6-bromo-1,2,3,4-tetrahydro-N-propyl-2-naphthaleneamine)carbamate. 23**

Propionyl chloride (18.5 ml) was added to (R)-2-amino-7-bromo-1,2,3,4-tetrahydronaphthalene (**22**) (*J. Org. Chem.* 1995, 4324) (43 g), triethylamine (31 ml) and dichloromethane. After 2 hours, the volume was concentrated under vacuum;
10 THF was added and concentrated under vacuum again. Water was added, cooled in an ice bath, and the solid filtered. Washing with water and drying under vacuum provided 51 g of a solid, m.p. 169-171° C. Borane dimethylsulfide complex (27 ml, 10M) was refluxed with this amide (51 g) in THF for 24 hours. Water was added, then 2 N hydrochloric acid. This was refluxed for an hour and was then basified
15 with 15% aqueous sodium hydroxide and extracted with methyl *t*-butylether. The ether layer was washed with water and brine, and was dried with sodium sulfate. Solvent was removed under vacuum to give 48 g of a dark oil. This amine and di-*tert*-butyl dicarbonate (44 g) were combined in THF. After 60 minutes, water (150 ml) was added and a catalytic amount of 4-dimethylaminopyridine. After 15 hours it
20 was partitioned between water and methyl *t*-butylether. The ether layer was washed with 2N hydrochloric acid, water, saturated aqueous sodium bicarbonate, and brine, and was dried with sodium sulfate. Solvent was removed under vacuum, and crystallization from hexane provided 59 g of **23** as a solid, m.p. 67-69° C.

25 **Procedure 15: *tert*-Butyl (R)-(6-aminomethyl-1,2,3,4-tetrahydro-N-propyl-2-naphthaleneamine)carbamate. 24**

tert-Butyllithium (1.7 M in pentane) (64 ml) was added to *tert*-butyl (R)-(6-bromo-1,2,3,4-tetrahydro-N-propyl-2-naphthaleneamine)carbamate (**23**) (20 g) in dry THF (125 ml) at -78° C. After 10 minutes, dry N,N-dimethylformamide (8 ml) was
30 added and the cold bath removed. After 90 minutes, the solution was partitioned between water and ether. The ether layer was washed with water and brine and was dried over sodium sulfate. Solvent was removed under vacuum to give 17 g of a solid, m.p. 88-91° C. Sodium borohydride (1.7 g) was added in portions to this aldehyde (14 g) in methanol in an ice bath. After 2 hours, water was added and the
35 solution concentrated under vacuum. The residue was partitioned between water and ether. The ether layer was washed with water and brine and was dried with

sodium sulfate. Solvent was removed under vacuum to give 14 g of the benzylic alcohol as a solid, m.p. 113-114° C. $[\alpha]_D = +53^\circ$ (25° C, CH₃OH, c = 0.96). Thionyl chloride (3.3 ml) was added slowly to this benzylic alcohol (13.6 g) in THF at 0° and then the ice bath was removed. After an hour, aqueous sodium bicarbonate was added and it was extracted with ether. The ether layer was washed with water and brine and was dried with sodium sulfate. Solvent was removed under vacuum and the residue was chromatographed on silica gel with dichloromethane/ hexane to give 9.6 g of the benzylic chloride as a solid, m.p. 90-93° C. $[\alpha]_D = +50^\circ$ (25° C, CH₃OH, c = 0.94). Sodim azide (8.7 g) and the benzylic chloride (9.0 g) were heated at 45° C in DMF for 18 hours, and then partitioned between ether/THF and water. The ether layer was washed with water and brine and was dried with sodium sulfate. Solvent was removed under vacuum to give 9.2 g of the azide as a solid, m.p. 73.5-75.0° C. $[\alpha]_D = +50^\circ$ (25° C, CH₃OH, c = 1.00). The azide (9.1 g) and palladium on carbon (0.5 g) were shaken in THF under 45 PSI hydrogen for 3 hours. The mixture was filtered through diatomaceous earth and solvent was removed under vacuum to give 7.9 g of **24** as a solid. An analytical sample was crystallized from hexane, m.p. 88-89° C. $[\alpha]_D = +53^\circ$ (25° C, CH₃OH, c = 1.00).

EXAMPLE 12: Procedure 16; (R)-4-Chloro-N-[[5,6,7,8-tetrahydro-6-(propylamino)-2-naphthalenyl]methyl]benzenesulfonamide. 25

tert-Butyl (R)-(6-aminomethyl-1,2,3,4-tetrahydro-N-propyl-2-naphthaleneamine)carbamate (**24**) (0.50 g), triethylamine (0.44 ml), 4-chlorobenzenesulfonyl chloride (0.36 g) and THF were stirred for 3 hours. The mixture was partitioned between aqueous sodium bicarbonate and ether/THF. The ether layer was washed with brine and dried with sodium sulfate. Solvent was removed and the residue was chromatographed on silica gel (dichloromethane/ethyl acetate/hexane) to give 0.77 g of a solid, m.p. 117-121° C. $[\alpha]_D = +32^\circ$ (25° C, CH₃OH, c = 0.78). To remove the BOC-protecting group, this solid was stirred with trifluoroacetic acid (5 ml) for 90 minutes and solvent was removed under vacuum. The mixture was partitioned between aqueous sodium bicarbonate and ether/THF. The ether layer was washed with brine and dried with sodium sulfate. Solvent was removed and gave 0.53 g of crystalline **25**, m.p. 145-147° C.

EXAMPLE 13: (R)-4-[3,5-Dimethyl-N-[[5,6,7,8-tetrahydro-6-(propylamino)-2-naphthalenyl]methyl]]isoxazolesulfonamide. 26

Using procedure 16, *tert*-butyl (R)-(6-aminomethyl-1,2,3,4-tetrahydro-N-

propyl-2-naphthaleneamine)carbamate (**24**) was treated with 3,5-dimethylisoxazole sulfonyl chloride to give crystalline **26** as its trifluoroacetic acid salt after deprotection of the BOC-group.

5 **EXAMPLE 14: Procedure 17. (R)-4-Chloro-N-[[5,6,7,8-tetrahydro-6-(dipropylamino)-2-naphthalenyl]methyl]benzenesulfonamide. 27**

Sodium triacetoxyborohydride (0.20 g) was added to (R)-4-chloro-N-[[5,6,7,8-tetrahydro-6-(propylamino)-2-naphthalenyl]methyl]benzenesulfonamide (**25**) (0.29 g), propionaldehyde (0.07 ml), glacial acetic acid (0.05 ml), and dichloromethane. After
10 3.5 hours, the mixture was partitioned between aqueous sodium bicarbonate and ether/THF. The ether layer was washed with water and brine and was dried with sodium sulfate. Solvent was removed under vacuum to give 0.31 g of **27** as a solid, m.p. 101-103° C. $[\alpha]_D = +42^\circ$ (25° C, CH₃OH, c = 0.93).

15 **EXAMPLE 15: Procedure 18. (R)-4-Chloro-N-[[5,6,7,8-tetrahydro-6-(propylamino)-2-naphthalenyl]methyl]benzamide. 28**

tert-Butyl (R)-(6-aminomethyl-1,2,3,4-tetrahydro-N-propyl-2-naphthaleneamine)carbamate (**24**) (0.50 g), triethylamine (0.44 ml), 4-chlorobenzoyl chloride (0.21 ml) and THF were stirred for 2.5 hours. The mixture was partitioned
20 between aqueous sodium bicarbonate and ether/THF. The ether layer was washed with brine and dried with sodium sulfate. Solvent was removed and the residue was chromatographed on silica gel (dichloromethane/ethyl acetate/hexane) to give 0.56 g of a solid, m.p. 154-155° C. $[\alpha]_D = +38^\circ$ (25° C, CH₃OH, c = 0.86). To remove the BOC-protecting group, this solid was stirred with trifluoroacetic acid (5 ml) for 60
25 minutes and the solvent was removed under vacuum. The residue was partitioned between aqueous sodium bicarbonate and ether/THF. The ether layer was washed with water and then dried with sodium sulfate. Solvent was removed under vacuum to give 0.34 g of **28** as a solid, m.p. 147-148° C. $[\alpha]_D = +49^\circ$ (25° C, CH₃OH, c = 0.87).

30

EXAMPLE 16: (R)-2-Acetyl-N-[[5,6,7,8-tetrahydro-6-(dipropylamino)-2-naphthalenyl]methyl]benzamide. 29

Using procedure 18, *tert*-Butyl (R)-(6-aminomethyl-1,2,3,4-tetrahydro-N-propyl-2-naphthaleneamine)carbamate (**24**) (0.3 g) can be treated with an
35 appropriate amount of 2-acetyl benzoyl chloride to give a white solid, m.p. 99° C. $[\alpha]_D = +35^\circ$ (25° C, CH₃OH, c = 0.95). This was stirred with trifluoroacetic acid (5

ml) for 90 minutes and solvent was removed under vacuum. Trituration with dry diethyl ether gave 0.28 g of crystalline **29** as its trifluoroacetic acid salt, m.p. 153-156° C. $[\alpha]_D = +45^\circ$ (25° C, CH₃OH, c = 0.86).

5 **EXAMPLE 17: (R)-4-Chloro-N-[[5,6,7,8-tetrahydro-6-(dipropylamino)-2-naphthalenyl]methyl]benzamide. 30**

Using procedure 17, (R)-4-chloro-N-[[5,6,7,8-tetrahydro-6-(propylamino)-2-naphthalenyl]methyl]benzamide (**28**) was converted to **30** as a solid, m.p. 141-142° C. $[\alpha]_D = +43^\circ$ (25° C, CH₃OH, c = 0.90).

10

EXAMPLE 18: Procedure 19. (R)-N-(4-Acetylphenyl)-N'-[[5,6,7,8-tetrahydro-6-(propylamino)-2-naphthalenyl]methyl]urea. 31

tert-Butyl (R)-(6-aminomethyl-1,2,3,4-tetrahydro-N-propyl-2-naphthaleneamine)carbamate (**24**) (0.30 g), 4-acetylphenyl isocyanate (0.16 g) and
15 THF were stirred for 6 hours. It was partitioned between aqueous sodium bicarbonate and ether/THF. The ether layer was washed with brine and dried with sodium sulfate. Solvent was removed and the residue was chromatographed on silica gel (dichloromethane/ethyl acetate/hexane) to give 0.35 g of a solid, m.p. 77-88° C. $[\alpha]_D = +34^\circ$ (25° C, CH₃OH, c = 0.83). This was stirred with trifluoroacetic acid
20 (5 ml) for 90 minutes and solvent was removed under vacuum. Trituration with dry diethyl ether gave 0.30 g of crystalline **31** as its trifluoroacetic acid salt, m.p. 200° C (decomposition).

25 **EXAMPLE 19: (R)-N-(4-Chlorophenyl)-N'-[[5,6,7,8-tetrahydro-6-(propylamino)-2-naphthalenyl]methyl]urea. 32**

Using procedure 19, *tert*-butyl (R)-(6-aminomethyl-1,2,3,4-tetrahydro-N-propyl-2-naphthaleneamine)carbamate (**24**) (0.70 g) was treated with 4-chlorophenyl isocyanate (0.36 g), then with trifluoroacetic acid to give 0.59 g of crystalline **32** as its trifluoroacetic acid salt, m.p. 192° C (decomposition).

30

EXAMPLE 20: (R)-N-(4-Nitrophenyl)-N'-[[5,6,7,8-tetrahydro-6-(propylamino)-2-naphthalenyl]methyl]urea. 33

Using procedure 19, *tert*-butyl (R)-(6-aminomethyl-1,2,3,4-tetrahydro-N-propyl-2-naphthaleneamine)carbamate (**24**) (0.30 g) was treated with 4-nitrophenyl
35 isocyanate (0.17 g), then with trifluoroacetic acid followed by basification and

extraction to give **33** as a solid.

Procedure 20: 4-(trifluoroacetylamino)heptan-1,6-diyne. 35

5 Triethylamine (19.5 g, 0.193 mol) was added to a solution of 2-(propyn-2-yl)-4-pentynoic acid (**34**, 25.0 g, 0.184 mol; *J. Chem. Soc., Perkin Trans. I*, 1215-1224 (1986)) in toluene (200 ml) with cooling. Diphenylphosphoryl azide (50.3 g, 0.184 mol) was added, and the mixture was stirred at room temperature for 15 minutes and heated on the steam bath until the evolution of gas ceased. Dry *t*-butanol (150
10 ml) was added, and the mixture was heated on the steam bath for 24 hours. The solvent was removed under vacuum, and the mixture was diluted with water and extracted twice with diethylether. The combined extracts were washed twice with 10% sodium carbonate solution and once with brine. The solution was dried
15 (MgSO₄), and the solvent was removed under vacuum to leave a solid. Purification by flash chromatography on silica gel eluting with ethyl acetate/hexane gave a white solid which was crystallized from hexane to give 4-(*t*-butyloxycarbonylamino)heptan-1,6-diyne as colorless crystals (m.p. 64-67°C).

4-(*t*-Butyloxycarbonylamino)heptan-1,6-diyne (30.0 g, 0.145 mol) was cooled in ice
20 and trifluoroacetic acid (80 ml) was added. A vigorous evolution of gas ensued. The mixture was stirred at room temperature for 30 minutes and excess trifluoroacetic acid was removed under vacuum. The residue was partitioned between diethylether and water, and the aqueous layer was extracted with 10% hydrochloric acid. The combined aqueous extracts were cooled in ice and basified with solid sodium
25 hydroxide and saturated with sodium chloride. The free base was extracted three times with diethylether. The combined extracts were washed with brine and dried (MgSO₄). The solvent was removed under vacuum to leave 4-aminoheptan-1,6-diyne as a light pink oil.

30 A solution 4-aminoheptan-1,6-diyne (14.63 g, 0.137 mol) and triethylamine (20.8 g, 0.206 mol) in dry tetrahydrofuran (100 ml) was cooled in ice and trifluoroacetic anhydride (37.5 g, 0.178 mol) was added with stirring over a 30 minute period. The mixture was stirred at 0°C for 1 hour and then allowed to stand at -15°C overnight. The mixture was stirred in an ice bath, and water (100 ml) was added dropwise.
35 The layers were separated, and the aqueous was extracted with diethylether. The combined organic extracts were washed with 10% hydrochloric acid, saturated

sodium bicarbonate solution (2X) and with brine. The solution was dried (MgSO_4), and the solvent was removed under vacuum to leave a solid. Crystallization from hexane/ethyl acetate gave **35** as slightly yellow crystals (m.p. 55-57°C).

5 Procedure 21: *N*-[5,6-Bis(acetyloxy)methyl]-2,3-dihydro-1*H*-inden-2-yl]-2,2,2-trifluoroacetamide. **36**

According to the procedure of Magnus *et al.* (*Tetrahed. Lett.*, **34**, 23-26 (1993)), a solution of 2-butyne-1,4-diol diacetate (34.03 g, 0.200 mol; *Syn. Comm.*, **9**, 789-797 (1979)) and tris(triphenylphosphine)rhodium chloride (2.78 g, 3.00 mmol) in argon
10 degassed absolute ethanol (100 ml) was heated to reflux and a solution of 4-(trifluoroacetyl amino)heptan-1,6-diyne (**35**, 20.32 g, 0.100 mol) in argon degassed absolute ethanol (70 ml) was added via a syringe pump over a period of 2.5 hours. The mixture was stirred under argon at 75-80°C for 8 hours and then at room
15 temperature for 10 hours, and the solvent was removed under vacuum to leave a dark oil. Purification by flash chromatography on silica gel eluting with ethyl acetate/hexane gave a light amber solid. Crystallization from ethyl acetate/hexane gave **36** as tan crystals (m.p. 98-100°C).

Procedure 22: 2-(dipropylamino)-5,6-bis(hydroxymethyl)indane. **37**

20 Potassium hydroxide (10.10 g, 0.180 mol) in water (35 ml) was added to a solution of *N*-[5,6-bis(acetyloxy)methyl]-2,3-dihydro-1*H*-inden-2-yl]-2,2,2-trifluoroacetamide (**36**, 20.1 g, 53.8 mmol) in methanol (200 ml) and heated to reflux for 2.5 hours. The solvent was removed under vacuum to leave a semi-solid. 1-Bromopropane (27.1 g, 0.220 mol), potassium carbonate (22.32 g, 0.162 mol), and
25 acetonitrile (100 ml) were added, and the mixture was stirred at reflux on the steam bath for 17 hours. 1-Bromopropane (6.8 g, 0.055 mol) was again added, and the reflux was continued for 4 hours. The mixture was diluted with ethyl acetate and washed with water and brine, and the solution was dried (MgSO_4). The solvent was removed under vacuum to leave a brown oil. Purification by flash chromatography
30 on silica gel eluting with tetrahydrofuran/ethyl acetate gave a solid. Crystallization from ethyl acetate/hexane gave **37** as white crystals (m.p. 111-113°C).

Procedure 23: 1,2,3,5,6,7-Hexahydro-*N,N*-dipropylcyclopent[*f*]isoindol-6-amine. **38**

35 Thionyl chloride (20 ml) was added to 2-(dipropylamino)-5,6-bis(hydroxymethyl)indane (**37**, 5.55 g, 20.0 mmol) with stirring, and the mixture

was refluxed on the steam bath for 1.75 hours. Excess thionyl chloride was removed under vacuum. The residue was dissolved in chloroform and the solvent was removed under vacuum. This process was repeated giving an amber solid. Crystallization from methanol/diethylether gave 2-(dipropylamino)-5,6-bis(chloromethyl)indane hydrochloride as off-white crystals (m.p. 208-210°C).

Allylamine (9.3 g, 0.16 mol) was added to 2-(dipropylamino)-5,6-bis(chloromethyl)indane (3.41 g, 10.9 mmol) with stirring. An exothermic reaction ensued which was controlled with a cool water bath. The mixture was stirred at room temperature for 18 hours and then refluxed on the steam bath for 4 hours. Excess allylamine was removed under vacuum, and the residue was diluted with 10% sodium carbonate solution and extracted twice with diethylether. The combined extracts were washed with brine and dried (MgSO₄). The solvent was removed under vacuum to leave an amber oil. Purification by flash chromatography on silica gel eluting with tetrahydrofuran/ethyl acetate gave 2-(propen-2-yl)-1,2,3,5,6,7-hexahydro-N,N-dipropylcyclopent[*f*]isoindol-6-amine as an amber oil.

A mixture of the 2-(propen-2-yl)-1,2,3,5,6,7-hexahydro-N,N-dipropylcyclopent[*f*]isoindol-6-amine (7.9 g, 26.5 mmol), *N,N'*-dimethylbarbituric acid (12.41 g, 79.5 mmol), palladium acetate (0.297 g, 1.32 mmol), and triphenylphosphine (0.695 g, 2.65 mmol) in dichloromethane (75 ml) was degassed with argon and heated to 40°C for 5 hours. The solvent was removed under vacuum, the residue diluted with 10% sodium carbonate solution, and extracted twice with diethylether. The combined extracts were washed with 10% sodium carbonate and extracted twice with 10% hydrochloric acid solution. An emulsion formed which was cleared by diluting with water and filtering through diatomaceous earth. The combined extracts were washed with diethylether and basified with solid sodium hydroxide. The free base was extracted three times with diethylether. The combined extracts were washed with brine and dried (Na₂SO₄). The solvent was removed under vacuum to leave **38** a brown solid, which could be crystallized with *p*-toluenesulfonic acid hydrate to give a gray-brown salt (m.p. 190-193°C).

EXAMPLE 21: 2-[(4-Chlorophenyl)sulfonyl]-1,2,3,5,6,7-hexahydro-N,N-dipropylcyclopent[*f*]isoindol-6-amine. **39**

Using procedure 9, crude 1,2,3,5,6,7-hexahydro-N,N-dipropylcyclopent[*f*]isoindol-6-amine (**38**, 0.42 g, 1.6 mmol) was treated with 4-

chlorobenzenesulfonyl chloride (0.343 g, 1.63 mmol). Purification by flash chromatography on silica gel using ethyl acetate/hexane and subsequent crystallization from methanol gave **39** as white crystals (m.p. 152-153°C).

5 EXAMPLE 22: 2-[(2-Chlorophenyl)sulfonyl]-1,2,3,5,6,7-hexahydro-N,N-dipropylcyclopent[*f*]isoindol-6-amine. 40

Using procedure 9, crude 1,2,3,5,6,7-hexahydro-N,N-dipropylcyclopent[*f*]isoindol-6-amine (**38**, 0.40 g, 1.5 mmol) was treated with 2-chlorobenzenesulfonyl chloride (0.36 g, 1.7 mmol). Purification by flash
10 chromatography on silica gel using ethyl acetate/hexane and crystallization from methanol gave **40** as tan crystals (m.p. 89-91°C).

EXAMPLE 23: 2-[(3-Chlorophenyl)sulfonyl]-1,2,3,5,6,7-hexahydro-N,N-dipropylcyclopent[*f*]isoindol-6-amine. 41

15 Using procedure 9, crude 1,2,3,5,6,7-hexahydro-N,N-dipropylcyclopent[*f*]isoindol-6-amine (**38**, 0.60 g, 2.3 mmol) was treated with 3-chlorobenzenesulfonyl chloride (0.54 g, 2.6 mmol). Purification by flash chromatography on silica gel using ethyl acetate in hexane and crystallization from methanol gave **41** as tan crystals (m.p. 113-114 °C).

20

EXAMPLE 24: 2-[(3-Cyanophenyl)sulfonyl]-1,2,3,5,6,7-hexahydro-N,N-dipropylcyclopent[*f*]isoindol-6-amine. 42

Using procedure 9, crude 1,2,3,5,6,7-hexahydro-N,N-dipropylcyclopent[*f*]isoindol-6-amine (**38**, 0.40 g, 1.5 mmol) was treated with 3-cyanobenzenesulfonyl chloride (0.35
25 g, 1.7 mmol). Purification by flash chromatography on silica gel using ethyl acetate in hexane and crystallization from methanol gave **42** as tan crystals (m.p. 134-135 °C).

EXAMPLE 25: 2-[3,5-Dimethylisoxazolyl]-4-sulfonyl]-1,2,3,5,6,7-hexahydro-N,N-dipropylcyclopent[*f*]isoindol-6-amine. 43

Using procedure 9, 1,2,3,5,6,7-hexahydro-N,N-dipropylcyclopent[*f*]isoindol-6-amine (**38**) was treated with 3,5-dimethylisoxazole-4-sulfonyl chloride. Crystallization from methanol gave **43** as gray crystals (m.p. 113-114 °C).

35 EXAMPLE 26: 2-[(Benz furazan)-4-sulfonyl]-1,2,3,5,6,7-hexahydro-N,N-dipropylcyclopent[*f*]isoindol-6-amine. 44

Using procedure 9, 1,2,3,5,6,7-hexahydro-N,N-dipropylcyclopent[*f*]isoindol-6-amine (38) was treated with benzofurazan-4-sulfonyl chloride. Crystallization from methanol gave 44 as gray-brown crystals (m.p. 115-118 °C).

5 **EXAMPLE 27: 2-[(2-(Benzoylaminomethyl)thiophene)-5-sulfonyl]-1,2,3,5,6,7-hexahydro-N,N-dipropylcyclopent[*f*]isoindol-6-amine. 45**

Using procedure 9, 1,2,3,5,6,7-hexahydro-N,N-dipropylcyclopent[*f*]isoindol-6-amine (38) was treated with 2-(benzoylaminomethyl)thiophene-5-sulfonyl chloride. Crystallization from methanol gave 45 as tan crystals (m.p. 160-161, 186-187 °C).

10

EXAMPLE 28: 2-[(2,3-Dichlorothiophene)-5-sulfonyl]-1,2,3,5,6,7-hexahydro-N,N-dipropylcyclopent[*f*]isoindol-6-amine. 46

Using procedure 9, 1,2,3,5,6,7-hexahydro-N,N-dipropylcyclopent[*f*]isoindol-6-amine (38) was treated with 2,3-dichlorothiophene-5-sulfonyl chloride.

15 Crystallization from methanol gave 46 as tan crystals (m.p. 150-151°C).

Procedure 30: *t*-Butyl [6,7-dihydro-3-[[benzyloxycarbonyl]aminomethyl]-5*H*-cyclopenta[*c*]pyridin-6-yl]carbamate. 55

A solution of benzyl chloroformate (17.1 g, 0.100 mol) in chloroform (50 ml)
20 was added dropwise at room temperature over a period of 10 minutes to a mixture of aminoacetonitrile hydrochloride (13.89 g, 0.150 mol) and sodium carbonate (21.2 g, 0.200 mol) in water (50 ml) and chloroform (20 ml) in a flask equipped with a mechanical stirrer. The mixture was stirred for 2 hours, diluted with water, and extracted twice with diethylether. The combined extracts were washed with brine
25 and dried (MgSO₄). The solvent was removed under vacuum to leave an oil. Crystallization from ethyl acetate/hexane gave *N*-benzyloxycarbonyl-2-aminoacetonitrile as colorless crystals (m.p. 61-62).

Using the procedure of Vollhardt (*J. Chem. Soc., Chem. Comm.*, 133-134 (1982)), a
30 solution of *N*-benzyloxy-2-aminoacetonitrile (1.91 g, 10.0 mmol) in *p*-xylene (50 ml) was heated under argon at 145°C. A solution of 4-(*t*-butyloxycarbonylamino)heptan-1,6-diyne (4.15 g, 20.0 mmol), *N*-benzyloxy-2-aminoacetonitrile (3.81 g, 20.0 mmol), and cyclopentadienylcobalt dicarbonyl (0.50 ml, ~2.8 mmol) in *p*-xylene (45 ml) under
35 argon was added via syringe pump to the heated xylene solution at the rate of 1.5 ml/hour. After the addition was complete, the solvent was removed under vacuum to leave a dark oil. Purification by flash chromatography on silica gel eluting with

ethyl acetate/hexane gave a tan solid. Crystallization from ethyl acetate/hexane gave **55** as tan crystals (m.p. 113-115°C).

Procedure 31: Phenylmethyl [[6-(dipropylamino)-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl]methyl]carbamate. **56**

Trifluoroacetic acid (25 ml) was added to *t*-butyl [6,7-dihydro-3-[[benzyloxycarbonyl]aminomethyl]-5H-cyclopenta[c]pyridin-6-yl]carbamate (**55**, 4.45 g, 11.2 mmol) at room temperature, and the mixture was stirred for 20 minutes. Excess trifluoroacetic acid was removed under vacuum, and the residue was partitioned between 1:1 tetrahydrofuran/diethylether and 5% sodium hydroxide solution. The aqueous solution was extracted twice more with 1:1 tetrahydrofuran/diethylether, and the combined extracts were washed with brine and dried (Na₂SO₄). The solvent was removed under vacuum to leave phenylmethyl [[6-amino-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl]methyl]carbamate as an amber oil.

A mixture of phenylmethyl [[6-amino-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl]methyl]carbamate (2.96 g, 10.4 mmol), 1-bromopropane (5.2 g, 4.2 mmol), and potassium carbonate (3.60 g, 26.0 mmol) in acetonitrile (30 ml) was stirred at reflux for 17 hours. The mixture was diluted with water and extracted twice with diethylether. The combined extracts were washed with brine and dried (MgSO₄). The solvent was removed under vacuum to leave a dark oil. Purification by flash chromatography on silica gel eluting with tetrahydrofuran/ethyl acetate gave a dark oil. The compound was treated with activated charcoal in ethyl acetate and filtered through diatomaceous earth to give **56** as an amber oil.

Procedure 32: 3-Aminomethyl-6-(dipropylamino)-6,7-dihydro-5H-cyclopenta[c]pyridine. **57**

A mixture of phenylmethyl [[6-(dipropylamino)-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl]methyl]carbamate (**56**, 1.35 g, 3.54 mmol) and 10% palladium on carbon in absolute ethanol was hydrogenated for 3 hours at 50 psi hydrogen. The mixture was filtered through diatomaceous earth, and the filtrate was evaporated under vacuum to leave **57** as a yellow oil.

EXAMPLE 29: 4-Chloro-N-[[6-(dipropylamino)-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl]methyl]benzenesulfonamide. **58**

Using procedure 9, 3-(aminomethyl)-6-(dipropylamino)-6,7-dihydro-5H-cyclopenta[c]pyridine (**57**, 0.29 g, 1.2 mmol) was treated with 4-chlorobenzenesulfonyl chloride (0.25 g, 1.2 mmol). After extraction, etc., purification by flash chromatography on silica gel eluting with tetrahydrofuran/ethyl acetate gave an off-white solid. Crystallization from ethyl acetate/hexane gave **58** as off-white crystals (m.p. 125-126.5 °C).

EXAMPLE 30: 2-Cyano-N-[[6-(dipropylamino)-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl]methyl]benzenesulfonamide. 59

Using procedure 9, 3-(aminomethyl)-6-(dipropylamino)-6,7-dihydro-5H-cyclopenta[c]pyridine (**57**, 0.42 g, 1.7 mmol) was treated with 2-cyanobenzenesulfonyl chloride (0.35 g, 1.7 mmol). Purification by flash chromatography on silica gel eluting with tetrahydrofuran in ethyl acetate gave an oil. Crystallization from ethyl acetate/hexane gave **59** as off-white crystals (m.p. 112-113 °C).

EXAMPLE 31: 4-Chloro-N-[[6-(dipropylamino)-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl]methyl]benzamide. 60

Using procedure 11, 3-(aminomethyl)-6-(dipropylamino)-6,7-dihydro-5H-cyclopenta[c]pyridine (**57**, 0.43 g, 1.7 mmol) was treated with 4-chlorobenzoyl chloride (0.32 g, 1.8 mmol). Purification by flash chromatography on silica gel eluting with tetrahydrofuran/ethyl acetate gave a tan solid. Crystallization from ethyl acetate/hexane gave **60** as gray crystals (m.p. 101.5-103 °C).

EXAMPLE 32: Procedure 33. N-(4-Chlorophenyl)-N'-[[6-(dipropylamino)-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl]methyl]urea. 61

3-(Aminomethyl)-6-(dipropylamino)-6,7-dihydro-5H-cyclopenta[c]pyridine (**57**, 0.42 g, 1.7 mmol) was added to a solution of 4-chlorophenyl isocyanate (0.28 g, 1.8 mmol) in toluene (5 ml). The mixture was stirred at room temperature for 18 hours, and the solvent was removed under vacuum to leave an oil. The compound was stirred for 10 minutes with 5% hydrochloric acid solution, basified with 10% sodium carbonate solution, and extracted twice with ethyl acetate. The combined extracts were washed with brine and dried (MgSO₄). The solvent was removed under vacuum to leave an oil. Purification by flash chromatography on silica gel eluting with tetrahydrofuran in ethyl acetate gave a light amber solid. Crystallization from ethyl acetate/hexane gave **61** as gray crystals (m.p. 120-121 °C).

EXAMPLE 33: N-(4-Cyanophenyl)-N'-[[6-(dipropylamino)-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl]methyl]urea. 62

Using procedure 33, 3-(aminomethyl)-6-(dipropylamino)-6,7-dihydro-5H-cyclopenta[c]pyridine (**57**, 0.495 g, 2.00 mmol) was treated with 4-cyanophenyl isocyanate (0.29 g, 2.0 mmol). Purification by flash chromatography on silica gel eluting with tetrahydrofuran/ethyl acetate gave a light amber oil. Crystallization from ethyl acetate/hexane gave **62** as tan crystals (m.p. 135.5-136.5 °C).

Procedure 34. 6-Propylamino-4,5,6,7-tetrahydrobenzothiazole. 64

Sodium cyanoborohydride (25 g) was added to 4,5,6,7-tetrahydrobenzothiazol-6-one (**63**) (*Helv. Chim. Acta* **1994** 1256) (14.5 g), propylamine (40 ml), glacial acetic acid (54 ml), methanol (500 ml) and THF (200 ml) in an ice bath. After 3.5 hours at room temperature, solvent was removed under vacuum and the residue was partitioned between aqueous sodium carbonate and ether/THF. The ether layer was washed with water and then 2N hydrochloric acid. This acid layer was basified and then extracted with diethyl ether/THF. This ether layer was washed with water and brine and was dried with sodium sulfate. Solvent was removed under vacuum to give 4.8 g of **64** as a liquid.

Procedure 35: tert-Butyl (2-formyl-4,5,6,7-tetrahydro-N-propyl-6-benzothiazolamine)carbamate. 65

6-Propylamino-4,5,6,7-tetrahydrobenzothiazole (**64**) (4.8 g) and di-tert-butyl dicarbonate (5.8 g) were combined in THF at 45° C. After 4.5 hours, solvent was removed and the residue was chromatographed on silica gel, eluting with ethyl acetate/hexane to give 5.8 g of a liquid after removal of solvent. n-Butyllithium (1.6 M in hexane, 7.4 ml) was added to this carbamate (3.0 g) in dry THF (25 ml) at -78° C. After 20 minutes, dry N,N-dimethylformamide (2.4 ml) was added and the cold bath removed. After 90 minutes, the solution was partitioned between water and ether. The ether layer was washed with water and brine and dried over sodium sulfate. The solvent was removed under vacuum and the residue was chromatographed on silica gel (ethyl acetate/hexane) to give 4.5 g of **65** as a liquid.

Procedure 36: tert-Butyl (2-hydroxyimino)methyl-4,5,6,7-tetrahydro-N-propyl-6-benzothiazolamine)carbamate. 66

Hydroxylamine hydrochloride (1.1 g) was added to tert-butyl (2-formyl-4,5,6,7-tetrahydro-N-propyl-6-benzothiazolamine)carbamate (**65**) (4.3 g), sodium hydroxide

(1.3 g) and water. After 5 minutes, carbon dioxide was bubbled through the solution. The mixture was partitioned between water and ether/THF. The ether layer was washed with water and brine and was dried with sodium sulfate. Solvent was removed and the residue was chromatographed on silica gel

5 (dichloromethane/ethyl acetate/hexane) to give 3.9 g of **66** as a solid.

Procedure 37: *tert*-Butyl (2-aminomethyl-4,5,6,7-tetrahydro-N-propyl-6-benzothiazolamine)carbamate. 67

Devarda's alloy (alloy of 50% copper, 45% aluminum, 5% zinc) (75 g) was
10 added to *tert*-Butyl (2-hydroxyimino)methyl-4,5,6,7-tetrahydro-N-propyl-6-benzothiazolamine)carbamate (**66**) (4.0 g), sodium hydroxide (2N aqueous, 200 ml) and methanol (50 ml) and heated at 42° C for 30 minutes. The mixture was extracted with diethyl ether/THF and the ether layer was washed with water and brine, and then dried with sodium sulfate. Solvent was removed under vacuum to
15 give 2.9 g of **67** as a liquid.

EXAMPLE 34: N-(4-Chlorophenyl)-N'-[[4,5,6,7-tetrahydro-6-(propylamino)-2-benzothiazolyl]methyl]urea. 68

Using procedure 19, *tert*-butyl (R)-(2-aminomethyl-4,5,6,7-tetrahydro-N-propyl-6-benzothiazolamine)carbamate (**67**) (0.90 g) was treated with 4-chlorophenyl isocyanate (0.46 g); then with trifluoroacetic acid to give 0.32 g of **68** as a solid, m.p. 125-130° C.

Procedure 38: 2-(Dipropylamino)-2,3-dihydro-6-(phenylmethoxy)-1H-inden-5-yl trifluoromethanesulfonate 70

Sodium hydride (0.96 g, 24 mmol) was washed with hexane under nitrogen and suspended in DMF (10 mL). 2-(Dipropylamino)-2,3-dihydro-6-hydroxy-1H-inden-5-yl trifluoromethanesulfonate (**69**, 7.6 g, 20 mmol) in DMF (30 mL) was added dropwise
30 at 0-5 °C over 30 min and the mixture stirred 30 min. Benzyl bromide (5.13 g, 30 mmol) in DMF (5 mL) was added and the resulting mixture was stirred 1 h. The reaction was quenched with saturated NaHCO₃ and extracted with EtOAc. The organic layer was washed with water, brine, dried (MgSO₄), filtered and concentrated to give the crude product. Chromatographic purification yielded pure
35 product **70** as an oil that was converted into the HCl salt and crystallized from EtOAc/MeOH/hexane to give a white solid (mp 162-163 °C)

**6-Butoxy-2-(dipropylamino)-2,3-dihydro-1H-inden-5-yl
trifluoromethanesulfonate 71**

5

Using procedure 38, 2-(dipropylamino)-2,3-dihydro-6-hydroxy-1H-inden-5-yl trifluoromethanesulfonate (**69**, 0.38 g, 1 mmol) was treated with bromobutane (0.27 g, 2 mmol). Chromatographic purification yielded pure product **71** as a oil which was converted into the HCl salt and crystallized from EtOAc/hexane to give a
10 white solid (mp 148-149 °C).

**2-(Dipropylamino)-2,3-dihydro-6-propoxy-1H-inden-5-yl
trifluoromethanesulfonate 72**

15

Using procedure 38, 2-(dipropylamino)-2,3-dihydro-6-hydroxy-1H-inden-5-yl trifluoromethanesulfonate (**69**, 1.9 g, 5 mmol) was treated with propylbromide (2.5 g, 20 mmol). Chromatographic purification yielded pure product **72** as a oil which was converted into the HCl salt and crystallized from EtOAc/hexane to give a white
20 solid (mp 169-170 °C)

**2-(Dipropylamino)-6-ethoxy-2,3-dihydro-1H-inden-5-yl
trifluoromethanesulfonate 73**

25 Using procedure 38, 2-(dipropylamino)-2,3-dihydro-6-hydroxy-1H-inden-5-yl trifluoromethanesulfonate (**69**, 1.9 g, 5 mmol) was treated with bromoethane (2.2 g, 20 mmol). Chromatographic purification yielded pure product **73** as a oil which was converted into the HCl salt and crystallized from EtOAc/hexane to give a white
30 solid (mp 181-182 °C)

Procedure 39: Methyl 2-(dipropylamino)-2,3-dihydro-6-(phenylmethoxy)-1H-indene-5-carboxylate 74

35 A mixture of 2-(Dipropylamino)-2,3-dihydro-6-(phenylmethoxy)-1H-indene-5-yl trifluoromethanesulfonate (**70**, 2.6 g, 5.6 mmol), palladium acetate (0.13 g, 0.56

mmol), 1,3-bis(diphenylphosphino-propane) (0.3 g, 0.73 mmol), triethylamine (0.7 mL, 6.3 mmol), methanol (6 mL), and DMF (18 mL) was heated at 60-70 °C with CO gas introduction. After 24 h, the reaction is quenched with saturated NaHCO₃, extracted with EtOAc, washed with water, brine, dried (MgSO₄), filtered and concentrated. Chromatographic purification yielded product **74** that was converted to the HCl salt and crystallized from EtOAc/MeOH to give a white solid (m.p. 181-182 °C)

Methyl 6-butoxy-2-(dipropylamino)-2,3-dihydro-1H-indene-5-carboxylate 75

Using procedure 39, 6-Butoxy-2-(dipropylamino)-2,3-dihydro-1H-inden-5-yl trifluoromethanesulfonate (**71**, 2.2 g, 5 mmol) was converted to methyl 6-butoxy-2-(dipropylamino)-2,3-dihydro-1H-indene-5-carboxylate **75** and crystallized from EtOAc/hexane as the HCl salt (m.p. 140-141 °C).

Methyl 2-(dipropylamino)-2,3-dihydro-6-propoxy-1H-indene-5-carboxylate 76

Using procedure 39, 2-(Dipropylamino)-2,3-dihydro-6-propoxy-1H-inden-5-yl trifluoromethanesulfonate (**72**, 2.96 g, 7 mmol) was converted to methyl 2-(dipropylamino)-2,3-dihydro-6-propoxy-1H-indene-5-carboxylate **76** and crystallized from EtOAc/hexane as the HCl salt (m.p. 175-176 °C)

Methyl 2-(dipropylamino)-6-ethoxy-2,3-dihydro-1H-indene-5-carboxylate 77

Using procedure 39, 2-(Dipropylamino)-6-ethoxy-2,3-dihydro-1H-inden-5-yl trifluoromethanesulfonate (**73**, 2.3 g, 5.7 mmol) was converted to methyl 2-(dipropylamino)-6-ethoxy-2,3-dihydro-1H-indene-5-carboxylate **77** and crystallized from EtOAc/hexane as the HCl salt (m.p. 168-169 °C)

EXAMPLE 35: Procedure 40: 2-(Dipropylamino)-2,3-dihydro-6-(phenylmethoxy)-1H-indene-5-carboxamide 78

To a solution of methyl 2-(dipropylamino)-2,3-dihydro-6-(phenylmethoxy)-1H-indene-

5-carboxylate (**74**, 0.95 g, 2.5 mmol) and formamide (1.1 g, 25 mmol) in DMF (10 mL) at 100 °C was added 25% sodium methoxide in methanol (2.5 mmol, 0.57 mL) dropwise. The mixture stirred for 2 h. The reaction was cooled to rt and quenched with water (100 mL). The resulting precipitate was stirred for 0.5 h and the solvent was removed via filtration. This solid was crystallized from EtOAc/MeOH to give a white solid that was converted into the HCl salt and crystallized from EtOAc/MeOH to give the title compound **78** as a white solid (m.p. 247-248 °C).

EXAMPLE 36: 6-Butoxy-2-(dipropylamino)-2,3-dihydro-1H-indene-5-carboxamide 79

Using procedure 40, methyl 6-butoxy-2-(dipropylamino)-2,3-dihydro-1H-indene-5-carboxylate (**75**, 1 g, 2.9 mmol) was converted to **79** and crystallized from EtOAc/MeOH as the HCl salt (m.p. 215-216 °C).

EXAMPLE 37: 2-(Dipropylamino)-2,3-dihydro-6-propoxy-1H-indene-5-carboxamide 80

Using procedure 40, methyl 2-(dipropylamino)-2,3-dihydro-6-propoxy-1H-indene-5-carboxylate (**76**, 1.1 g, 3.5 mmol) was converted to **80** and crystallized from EtOAc/EtOH as the HCl salt (m.p. 238-239 °C).

EXAMPLE 38: 2-(Dipropylamino)-6-ethoxy-2,3-dihydro-1H-indene-5-carboxamide 81

Using procedure 40, methyl 2-(dipropylamino)-6-ethoxy-2,3-dihydro-1H-indene-5-carboxylate (**77**, 1.1 g, 3.5 mmol) was converted to **81** and crystallized from EtOAc/MeOH as the HCl salt (m.p. 236-237 °C).

EXAMPLE 39: Procedure 41: 6-Butoxy-2-(dipropylamino)-2,3-dihydro-N-methyl-1H-indene-5-carboxamide 82

To a mixture of methyl 6-butoxy-2-(dipropylamino)-2,3-dihydro-1H-indene-5-carboxylate (**75**, 0.35 g, 1 mmol) and N-methylformamide (0.59 g, 10 mmol) in DMF (10 mL) at 100 °C and 25% was added sodium methoxide in methanol (0.22 mL, 1 mmol) dropwise over a period of 10 min. The resulting mixture is cooled to room

temperature and quenched with water (100 mL). The resulting solid was purified by chromatography to give an oil that was converted into the HCl salt and crystallized from EtOAc/MeOH to yield the title compound **82** as a white solid (m.p. 129-130 °C).

5 **EXAMPLE 40: 6-Ethoxy-2-(dipropylamino)-2,3-dihydro-N-methyl-1H-indene-5-carboxamide 83**

Using procedure 41, methyl 2-(dipropylamino)-6-ethoxy-2,3-dihydro-1H-indene-5-carboxylate (**77**, 0.32 g, 1 mmol) was treated with N-methylformamide (0.58 mL, 10
10 mmol). Chromatographic purification yielded pure product **83** as a oil which was converted into the HCl salt and crystallized from EtOAc/MeOH to give a white solid (m.p. 156-159 °C).

EXAMPLE 41: 2-(Dipropylamino)-6-ethoxy-2,3-dihydro-N-(phenylmethyl)-1H-indene-5- carboxamide 84
15

Using procedure 41, methyl 2-(dipropylamino)-6-ethoxy-2,3-dihydro-1H-indene-5-carboxylate (**77**, 0.32 g, 1 mmol) was treated with N-benzylformamide (1.35 g, 10
20 mmol). Chromatographic purification yielded pure product **84** as a oil which was converted into the HCl salt and crystallized from EtOAc to give a white solid (m.p. 219-221 °C).

EXAMPLE 42: Procedure 42: 2-(Dipropylamino)-6-ethoxy-N-(2-fluoroethyl)-2,3-dihydro-1H-indene- 5-carboxamide 85
25

Sodium hydride (0.05 g, 1.2 mmol) was washed with hexane under nitrogen and suspended in DMF (5 mL). 2-(Dipropylamino)-6-ethoxy-2,3-dihydro-1H-indene-5-carboxamide (**81**, 0.15 g, 0.5 mmol) in DMF (5 mL) was added dropwise at 0-5 °C over 30 min and the mixture stirred 30 min. 1-Bromo-2-fluoroethane (0.26 g, 2
30 mmol) in DMF (5 mL) was added and the resulting mixture was stirred 3 h. The reaction was quenched with saturated NaHCO₃ and extracted with EtOAc. The organic layer is washed with water, brine, dried (MgSO₄), filtered and concentrated to give crude product. Chromatographic purification yielded pure product **85** as an oil that was converted into the HCl salt and crystallized from EtOAc/hexane/MeOH
35 to give a white solid (m.p. 158-159 °C).

Procedure 43: 2-(Dipropylamino)-2,3-dihydro-6-hydroxy-1H-indene-5-carboxamide 87

To a solution of methyl 2-(dipropylamino)-2,3-dihydro-6-hydroxy-1H-indene-5-carboxylate (**86**, 0.93 g, 2.9 mmol) and formamide (1.2 mL, 29 mmol) in DMF (20 mL) at 100 °C was added 25% sodium methoxide in methanol (1.3 mL, 5.8 mmol) dropwise. The mixture stirred for 4 h. The reaction was quenched with saturated NaHCO₃ and extracted with EtOAc. The organic layer is washed with water, brine dried (MgSO₄), filtered and concentrated to give the crude product.

Chromatographic purification yielded pure product as an oil that was converted into the HCl salt and crystallized from EtOAc/MeOH to give the title compound **87** as a white solid (m.p. 266-267 °C).

EXAMPLE 43: Procedure 44: 2-(Dipropylamino)-6-(2-fluoroethoxy)-2,3-dihydro-1H-indene-5-carboxamide 88

A mixture of 2-(Dipropylamino)-2,3-dihydro-6-hydroxy-1H-indene-5-carboxamide (**87**, 0.14 g, 0.5 mmol), potassium carbonate (0.2 g, 1.5 mmol), 1-bromo-2-fluoroethane (0.19 g, 1.5 mmol) in DMF (10 mL) was stirred at room temperature for 5 h. The mixture was quenched with water, and extracted with EtOAc. The organic layer was washed with brine, dried (MgSO₄), filtered and concentrated. Chromatographic purification yielded a pale yellow solid which was converted into the HCl salt and crystallized from EtOAc/MeOH to give the title compound **88** as an off-white solid (m.p. 232-233 °C).

EXAMPLE 44: 2-(Dipropylamino)-6-(3-fluoropropoxy)-2,3-dihydro-1H-indene-5-carboxamide 89

Using procedure 44, 2-(Dipropylamino)-2,3-dihydro-6-hydroxy-1H-indene-5-carboxamide (**87**, 0.19 g, 0.7 mmol) was treated with 1-bromo-3-fluoropropane (0.296 g, 2.1 mmol). Chromatographic purification yielded pure product **89** as a oil which was converted into the HCl salt and crystallized from EtOAc/MeOH to give a white solid (m.p. 219-220 °C).

EXAMPLE 45: 2-(Dipropylamino)-6-ethoxy-N-ethyl-2,3-dihydro-1H-indene-5-carboxamide 90

Using procedure 44, 2-(Dipropylamino)-2,3-dihydro-6-hydroxy-1H-indene-5-carboxamide (**87**, 0.36 g, 1.15 mmol) was treated with bromoethane (0.38 g, 3.45 mmol). Chromatographic purification yielded pure product as a oil **90** which was converted into the HCl salt and crystallized from EtOAc/MeOH to give a white solid (m.p. 145-146 °C).

10 Procedure 45: 2-(dipropylamino)-2,3-dihydro-1H-indene-5,6-dicarboxylate 92

The dimethyl 2-(dipropylamino)-2,3-dihydro-1H-indene-5,6-dicarboxylate (**91**, 10.0 g, 30.0 mmol) was refluxed at 70°C with NaOH (2.4 g, 60.0 mmol) in 1:3 H₂O/MeOH (100 mL) for 3 h. The reaction was concentrated and lyophilized. The resulting solid was heated in THF/MeOH (1:1) and allowed to cool overnight. The resulting solid **92** was obtained via filtration and dried (m.p. >300°C).

EXAMPLE 46: Procedure 46: 6-(Dipropylamino)-6,7-dihydrocyclopent[f]isoindole-1,3(2H,5H)-dione 93

20

A solution of 2-(dipropylamino)-2,3-dihydro-1H-indene-5,6-dicarboxylate (**92**, 3.00g, 8.6 mmol), (NH₄)OAc (6.63 g, 86.0 mmol), and conc. HCl (1.7 mL) in glacial HOAc (200 mL) was refluxed at 119°C for 20 h. The reaction was cooled, concentrated, and azeotroped with toluene to give a white solid. The residue was diluted with H₂O, basified with sat'd NaHCO₃ to pH > 9, and filtered through a sintered glass funnel. The collected solid was diluted with MeOH and azeotroped numerous times with toluene until dry. The solid was dissolved in hot MeOH, filtered through filter paper and recrystallized from additional hot MeOH to give **93** as a tan solid. The solid was converted to the HCl salt and recrystallized from hot MeOH/EtOAc to give a white solid (m.p. 290-291°C).

30

EXAMPLE 47: Procedure 47. 6-(Dipropylamino)-3,5,6,7-tetrahydrocyclopent[f]isoindol-1(2H)- n 94

35

(Ref. Brewster, J.H.; Fusco A. M. *J.Org. Chem.* , 28, 501-503 (1963)) A solution of

6-(dipropylamino)-6,7-dihydrocyclopent[*f*]isoindole-1,3(2H,5H)-dione **93** (0.45 g, 1.6 mmol) in glacial HOAc (50 mL) was treated with Zinc dust (1.05 g, 16.0 mmol) then refluxed at 113°C for 24 h. The reaction was cooled to r.t., diluted with MeOH and filtered through a pad of celite. The filtrate was concentrated and the residue was diluted with H₂O, basified with sat'd Na₂CO₃, and extracted with CH₂Cl₂. The organic layers were washed with brine, dried (MgSO₄), and concentrated. The resulting solid was purified using silica gel, eluting with 2:1 heptane/acetone to give **94** as a white solid (m.p. 206-208°C).

EXAMPLE 48: Procedure 48. 6-(Dipropylamino)-2-ethyl-6,7-dihydrocyclopent[*f*]isoindole-1,3(2H,5H)-dione 95

To a solution of 6-(dipropylamino)-6,7-dihydrocyclopent[*f*]isoindole-1,3(2H,5H)-dione (**93**, 0.15 g, 0.52 mmol) in DMF (10 mL) at 0°C was added anhydrous K₂CO₃ (0.14 g, 1.04 mmol) followed by ethyl bromide (0.06 mL, 0.79 mmol). The reaction was stirred at 0°C for 2 hr then allowed to warm to r.t. Continued stirring overnight then quenched with H₂O. The solution was extracted with CH₂Cl₂ and the organic layers were washed with brine, dried (MgSO₄), and concentrated. The residue was further concentrated on the high vac to remove any excess DMF and the resulting greenish solid was purified using silica gel, eluting with 3:1 hexane/acetone to give **95** as an off-white solid. The solid was converted to an HCl salt and recrystallized from hot MeOH/EtOAc to give **95** as a white solid (m.p. 225-230°C).

EXAMPLE 49: 6-(Dipropylamino)-6,7-dihydro-2-propylcyclopent[*f*]isoindole-1,3(2H,5H)-dione 96

Using procedure 48, 6-(dipropylamino)-6,7-dihydrocyclopent[*f*]isoindole-1,3(2H,5H)-dione (**93**, 0.15 g, 0.52 mmol) was treated with 1-bromopropane (0.07 mL, 0.78 mmol). Purification via silica gel, eluting with 3:1 hexane/acetone, afforded a solid that was converted to an HCl salt and recrystallized from hot MeOH/EtOAc to give **96** as a white solid (m.p. 217-218°C).

EXAMPLE 50: 4-[[6-(Dipropylamino)-3,5,6,7-tetrahydro-1,3-dioxocyclopent[*f*]isoindol-2(1H)-yl]methyl]benz nitrile 97

Using procedure 48, 6-(dipropylamino)-6,7-dihydrocyclopent[*f*]isoindole-1,3(2H,5H)-

dione (**93**, 0.12 g, 0.4 mmol) was treated with alpha-bromo-p-tolunitrile (0.08 mL, 0.4 mmol). Purification using silica gel, eluting with 3:1 hexane/acetone, afforded a solid that was converted to an HCl salt and recrystallized from hot MeOH/EtOAc to give **97** as a white solid (m.p. 263-264°C).

5

EXAMPLE 51: 2-(1H-Benzotriazol-1-ylmethyl)-6-(dipropylamino)- 6,7-dihydrocyclopent[f]isoindole-1,3(2H,5H)-dione 98

Using procedure 48, 6-(dipropylamino)-6,7-dihydrocyclopent[f]isoindole-1,3(2H,5H)-
10 dione (**93**, 0.14 g, 0.5 mmol) was treated with 1-(chloromethyl)-1H-benzotriazole (0.08 g, 0.5 mmol). Purification using silica gel, eluting with 3:1 hexane/acetone, afforded a solid that was converted to an HCl salt and recrystallized from hot MeOH/EtOAc to give **98** as a white solid (m.p. 254-256°C).

15 **EXAMPLE 52: 6-(Dipropylamino)-6,7-dihydro-2-[(2-methyl-5-thiazolyl)methyl] cyclopent[f]isoindole-1,3(2H,5H)-dione 99**

Using procedure 48, 6-(dipropylamino)-6,7-dihydrocyclopent[f]isoindole-1,3(2H,5H)-
dione (**93**, 0.14 g, 0.5 mmol) was treated with 4-chloromethyl-2-methylthiazole
20 hydrochloride (0.18 g, 1.0 mmol). Purification using silica gel, eluting with 4:1 hexane/acetone + 0.1% MeOH, afforded a solid that was converted to an HCl salt and recrystallized from hot MeOH/EtOAc to give **99** as a white solid (m.p. 235-236°C).

25 **EXAMPLE 53: 6-(Dipropylamino)-6,7-dihydro-2-(1,2,4-oxadiazol-3-ylmethyl) cyclopent[f]isoindole-1,3(2H,5H)-dione 100**

Using procedure 48, 6-(dipropylamino)-6,7-dihydrocyclopent[f]isoindole-1,3(2H,5H)-
dione (**93**, 0.14 g, 0.5 mmol) was treated with 3-(chloromethyl)-1,2,4-oxadiazole
30 (0.09 g, 0.75 mmol). Purification using silica gel, eluting with 7:1 CH₂Cl₂/acetone, afforded a solid that was converted to an HCl salt and recrystallized from CH₂Cl₂/Et₂O to give **100** as a white solid (m.p. 190-191°C).

EXAMPLE 54: Procedure 49. 6-(Dipropylamino)-2-[(4-fluorophenyl)methyl]-
35 **6,7- dihydrocyclopent[f]isoindole-1,3(2H,5H)-dione 101**

(O'Reilly, N.J., Derwin, W.S., Fertel, L.B., Lin, H.C., *Synlett.*, (1990) 609-610.) A solution of 2-(dipropylamino)-2,3-dihydro-1H-indene-5,6-dicarboxylate (**92**, 0.35 g, 1.0 mmol) and 4-fluorobenzylamine (0.15 mL, 1.3 mmol) in glacial HOAc (30 mL) was refluxed at 113°C. After 4 h, the reaction was cooled to r.t., concentrated, then
5 azeotroped with toluene. The residue was diluted with water and basified with sat'd Na₂CO₃ (or sat'd NaHCO₃) to pH > 12. The solution was extracted with CH₂Cl₂ and the organic layers were washed with brine, dried (MgSO₄), and concentrated. The residue was purified by using silica gel, eluting with 4:1 CH₂Cl₂/acetone + 0.1 % MeOH, to give **101** as a light yellow oil that was converted to an HCl salt and
10 recrystallized from MeOH/EtOAc to give a white solid (m.p. 251-253°C).

EXAMPLE 55: 2-[(4-Chlorophenyl)methyl]-6-(dipropylamino)-6,7-dihydrocyclopent[f]isoindole-1,3(2H,5H)-dione 102

15 Using procedure 49, 2-(dipropylamino)-2,3-dihydro-1H-indene-5,6-dicarboxylate (**92**, 0.35 g, 1.0 mmol) was treated with 4-chlorobenzylamine (0.17 mL, 1.4 mmol). Purification using silica gel, eluting with 5:1 hexane/acetone, afforded an oil that was converted to an HCl salt and recrystallized from hot MeOH/EtOAc to give **102** as a white solid (m.p. 260-261°C).

20

EXAMPLE 56: 6-(Dipropylamino)-6,7-dihydro-2-[(2-methoxyphenyl)methyl]cyclopent[f]isoindole-1,3(2H,5H)-dione 103

Using procedure 49, 2-(dipropylamino)-2,3-dihydro-1H-indene-5,6-dicarboxylate (**92**,
25 0.35 g, 1.0 mmol) was treated with *o*-methoxybenzylamine (0.18 mL, 1.4 mmol). Purification using silica gel, eluting with 5:1 CH₂Cl₂/acetone, afforded an oil that was converted to an HCl salt and recrystallized from hot MeOH/EtOAc to give **103** as a white solid (m.p. 205°C).

30 **EXAMPLE 57: 6-(Dipropylamino)-6,7-dihydro-2-[(3-methoxyphenyl)methyl]cyclopent[f]isoindole-1,3(2H,5H)-dione 104**

Using procedure 49, 2-(dipropylamino)-2,3-dihydro-1H-indene-5,6-dicarboxylate (**92**, 0.35 g, 1.0 mmol) was treated with *m*-methoxybenzylamine (0.17 mL, 1.3 mmol).
35 Purification using silica gel, eluting with 3:1 hexane/acetone, afforded an oil that was converted to an HCl salt and recrystallized from hot MeOH/EtOAc to give **104**

as a white solid (m.p. 247-248°C).

EXAMPLE 58: 6-(Dipropylamino)-6,7-dihydro-2-[(4-methoxyphenyl)methyl]cyclopent[f]isoindole-1,3(2H,5H)-dione 105

5

Using procedure 49, 2-(dipropylamino)-2,3-dihydro-1H-indene-5,6-dicarboxylate (**92**, 0.10 g, 0.28 mmol) was treated with *p*-methoxybenzylamine (0.05 mL, 0.4 mmol). Purification using silica gel, eluting with 5:1 CH₂Cl₂/acetone, afforded an oil that was converted to an HCl salt and recrystallized from EtOAc to give **105** as a white solid (m.p. 255-256°C).

10

EXAMPLE 59: 2-[(3,4-Dimethoxyphenyl)methyl]-6-(dipropylamino)-6,7-dihydrocyclopent[f]isoindole-1,3(2H,5H)-dione 106

Using procedure 49, 2-(dipropylamino)-2,3-dihydro-1H-indene-5,6-dicarboxylate (**92**, 0.35 g, 1.0 mmol) was treated with veratrylamine (0.20 mL, 1.3 mmol). Purification using silica gel, eluting with 3:1 hexane/acetone, afforded an oil that was converted to an HCl salt and recrystallized from hot MeOH/EtOAc to give **106** as a white solid (m.p. 233-235°C).

20

EXAMPLE 60: 6-(Dipropylamino)-6,7-dihydro-2-[[4-(trifluoromethoxy)phenyl]methyl]cyclopent[f]isoindole-1,3(2H,5H)-dione 107

Using procedure 49, 2-(dipropylamino)-2,3-dihydro-1H-indene-5,6-dicarboxylate (**92**, 0.35 g, 1.0 mmol) was treated with 4-trifluoromethoxybenzylamine (0.25 mL, 1.3 mmol). Purification using silica gel, eluting with 3:1 CH₂Cl₂/acetone, afforded an oil that was converted to an HCl salt and recrystallized from hot MeOH/EtOAc to give **107** as a white solid (m.p. 233-235°C).

30

EXAMPLE 61: 6-(Dipropylamino)-6,7-dihydro-2-(2-phenylethyl)cyclopent[f]isoindole-1,3(2H,5H)-dione 108

Using procedure 49, 2-(dipropylamino)-2,3-dihydro-1H-indene-5,6-dicarboxylate (**92**, 0.35 g, 1.0 mmol) was treated with 4-trifluoromethyl-benzylamine (0.2 mL, 1.4 mmol). Purification using silica gel, eluting with 4:1 CH₂Cl₂/acetone, afforded an oil

35

that was converted to an HCl salt and recrystallized from hot MeOH/EtOAc to give **108** as a white solid (m.p. 229-230°C).

EXAMPLE 62: 4-[[6-(Dipropylamino)-3,5,6,7-tetrahydro-1,3-dioxocyclopent[f]isoindol-2(1H)-yl]methyl]benzenesulfonamide 109

Using procedure 49, 2-(dipropylamino)-2,3-dihydro-1H-indene-5,6-dicarboxylate (**92**, 0.35 g, 1.0 mmol) was treated with *p*-aminomethylbenzenesulfonamide (0.31 g, 1.4 mmol). Purification using silica gel, eluting with 4:1 CH₂Cl₂/acetone, afforded a solid that recrystallized from CH₂Cl₂/Et₂O/hexane to give **109** as a white solid (m.p. 190-194°C).

EXAMPLE 63: Methyl 4-[[6-(dipropylamino)-3,5,6,7-tetrahydro-1,3-dioxocyclopent[f]isoindol-2(1H)-yl]methyl]benzoate 110

The 4-(aminomethyl)benzoic acid methyl ester was obtained from the conversion of 4-(aminomethyl)benzoic acid via esterification using MeOH/H₂SO₄. The ester was converted to the HCl salt and recrystallized from EtOAc (m.p. 238-240°C).

Using procedure 49, 2-(dipropylamino)-2,3-dihydro-1H-indene-5,6-dicarboxylate (**92**, 0.35 g, 1.0 mmol) was treated with 4-(aminomethyl)benzoic acid methyl ester (0.28 g, 1.4 mmol). Purification using silica gel, eluting with 4:1 CH₂Cl₂/acetone, afforded an oil that was converted to an HCl salt and recrystallized from hot MeOH/EtOAc to give **110** as a white solid (m.p. 244-246°C).

EXAMPLE 64: 4-[[6-(Dipropylamino)-3,5,6,7-tetrahydro-1,3-dioxocyclopent[f]isoindol-2(1H)-yl]methyl]benzamide 111

The 4-(aminomethyl)benzamide was obtained from the conversion of 4-(aminomethyl)benzoic acid methyl ester via reaction with NH₄OH using the procedure of Clifton, J.E., et al., *J. Med. Chem.*, **1982**, *25*, 670-679. The amide was converted to the HCl salt and recrystallized from MeOH/EtOAc (m.p. 244-249°C).

Using procedure 49, 2-(dipropylamino)-2,3-dihydro-1H-indene-5,6-dicarboxylate (**92**, 0.35 g, 1.0 mmol) was treated with 4-(aminomethyl)benzamide (0.26 g, 1.4 mmol).

Purification using silica gel, eluting with 19:1 CH₂Cl₂/MeOH, afforded an oil that was converted to an HCl salt and recrystallized from hot MeOH to give 111 as a white solid (m.p. 294°C).

5 **EXAMPLE 65: 6-(Dipropylamino)-6,7-dihydro-2-(2-phenylethyl)cyclopent[f]isoindole- 1,3(2H,5H)-dione 112**

Using procedure 49, 2-(dipropylamino)-2,3-dihydro-1H-indene-5,6-dicarboxylate (**92**, 0.35 g, 1.0 mmol) was treated with phenethylamine (0.16 mL, 1.3 mmol).

- 10 Purification using silica gel, eluting with 3:1 CH₂Cl₂/acetone, afforded an oil that was converted to an HCl salt and recrystallized from hot MeOH/EtOAc to give **112** as a white solid (m.p. 235-240°C).

15 **EXAMPLE 66: 6-(Dipropylamino)-6,7-dihydro-2-[2-(4-methoxyphenyl)ethyl]cyclopent[f]isoindole-1,3(2H,5H)-dione 113**

Using procedure 49, 2-(dipropylamino)-2,3-dihydro-1H-indene-5,6-dicarboxylate (**92**, 0.35 g, 1.0 mmol) was treated with 4-methoxyphenethylamine (0.19 mL, 1.3 mmol).

- 20 Purification using silica gel, eluting with 3:1 hexane/acetone, afforded an oil that was converted to an HCl salt and recrystallized from hot MeOH/EtOAc to give **113** as a white solid (m.p. 211-215°C).

25 **EXAMPLE 67: 6-(Dipropylamino)-6,7-dihydro-2-(3-phenylpropyl)cyclopent[f]isoindole- 1,3(2H,5H)-dione 114**

Using procedure 49, 2-(dipropylamino)-2,3-dihydro-1H-indene-5,6-dicarboxylate (**92**, 0.35 g, 1.0 mmol) was treated with 3-phenylpropylamine (0.19 mL, 1.4 mmol).

- 30 Purification using silica gel, eluting with 9:1 CH₂Cl₂/acetone, afforded an oil that was converted to an HCl salt and recrystallized from hot MeOH/EtOAc to give **114** as a white solid (m.p. 222-223°C).

EXAMPLE 68: 6-(Dipropylamino)-6,7-dihydro-2-(2-pyridinylmethyl)cyclopent[f]isoindole- 1,3(2H,5H)-dione 115

- 35 Using procedure 49, 2-(dipropylamino)-2,3-dihydro-1H-indene-5,6-dicarboxylate (**92**, 0.35 g, 1.0 mmol) was treated with 2-aminomethylpyridine (0.4 mL, 4.0 mmol).

Purification via using silica gel, eluting with 2:1 CH₂Cl₂/acetone, afforded an oil that was converted to an HCl salt and recrystallized from hot MeOH/EtOAc to give 115 as a white solid (m.p. 130-135°C).

5 **EXAMPLE 69: 6-(Dipropylamino)-6,7-dihydro-2-(3-pyridinylmethyl)cyclopent[f]isoindole- 1,3(2H,5H)-dione 116**

Using procedure 49, 2-(dipropylamino)-2,3-dihydro-1H-indene-5,6-dicarboxylate (**92**, 0.35 g, 1.0 mmol) was treated with 3-aminomethylpyridine (0.14 mL, 1.4 mmol).

- 10 Purification using silica gel, eluting with 19:1 CH₂Cl₂/MeOH sat'd with NH₃, afforded an oil that was converted to an HCl salt and recrystallized from hot MeOH/EtOAc to give **116** as a white solid (m.p. 141-146°C).

15 **EXAMPLE 70: 6-(Dipropylamino)-6,7-dihydro-2-(4-pyridinylmethyl)cyclopent[f]isoindole- 1,3(2H,5H)-dione 117**

Using procedure 49, 2-(dipropylamino)-2,3-dihydro-1H-indene-5,6-dicarboxylate (**92**, 0.35 g, 1.0 mmol) was treated with 4-aminomethylpyridine (0.14 mL, 1.4 mmol).

- 20 Purification using silica gel, eluting with 3:1 CH₂Cl₂/acetone, afforded an oil that was converted to an HCl salt and recrystallized from hot MeOH/EtOAc to give **117** as a white solid (m.p. 283-284°C).

25 **EXAMPLE 71: 6-(Dipropylamino)-6,7-dihydro-2-[2-(1H-imidazol-4-yl)ethyl]cyclopent[f]isoindole-1,3(2H,5H)-dione 118**

- Using procedure 49, 2-(dipropylamino)-2,3-dihydro-1H-indene-5,6-dicarboxylate (**92**, 0.35 g, 1.0 mmol) was treated with histamine (0.16 g, 1.4 mmol). Purification using silica gel, eluting with 9:1 CH₂Cl₂/MeOH, afforded a solid that was converted to an HCl salt and recrystallized from hot MeOH/EtOAc to give **118** as a white solid (m.p. 190-191°C).
- 30

EXAMPLE 72: 6-(Dipropylamino)-6,7-dihydro-2-(2-thienylmethyl)cyclopent[f]isoindole- 1,3(2H,5H)-dione 119

- 35 Using procedure 49, 2-(dipropylamino)-2,3-dihydro-1H-indene-5,6-dicarboxylate (**92**, 0.35 g, 1.0 mmol) was treated with 2-thiophene-methylamine (0.13 mL, 1.3 mmol).

Purification using silica gel, eluting with 3:1 CH₂Cl₂/acetone, afforded an oil that was converted to an HCl salt and recrystallized from hot MeOH/EtOAc to give **119** as a white solid (m.p. 220-225°C).

5 **EXAMPLE 73: 6-(Dipropylamino)-6,7-dihydro-2-methylcyclopent[f]isoindole-1,3(2H,5H)- dione 120**

Using procedure 49, 2-(dipropylamino)-2,3-dihydro-1H-indene-5,6-dicarboxylate (**92**, 0.3 g, 1.0 mmol) was treated with methylamine hydrochloride (1.35 g, 20.0 mmol).

10 Purification on silica gel, eluting with 2:1 hexane/acetone, afforded an oil that was converted to an HCl salt and recrystallized from EtOAc/2-propanol to give **120** as a white solid (m.p. 245-246°C).

EXAMPLE 74: 6-(Dipropylamino)-6,7-dihydro-2-phenylcyclopent[f]isoindole-
15 **1,3(2H,5H)- dione 121**

Using procedure 49, 2-(dipropylamino)-2,3-dihydro-1H-indene-5,6-dicarboxylate (**92**, 0.3 g, 1.0 mmol) was treated with aniline (0.11 g, 1.2 mmol). Purification on silica gel, eluting with 2:1 hexane/acetone, afforded a solid that was converted to an HCl
20 salt and recrystallized from EtOAc/2-propanol to give **121** as a white solid (m.p. 241-242°C).

EXAMPLE 75: 4-[6-(Dipropylamino)-3,5,6,7-tetrahydro-1,3-
25 **dioxocyclopent[f]isoindol- 2(1H)-yl]benzamide 122**

Using procedure 49, 2-(dipropylamino)-2,3-dihydro-1H-indene-5,6-dicarboxylate (**92**, 0.3 g, 1.0 mmol) was treated with 4-aminobenzamide (1.4 g, 10.0 mmol).
Purification on silica gel, eluting with 9:1 CH₂Cl₂/MeOH sat'd w/ NH₃, afforded a
solid that was converted to an HCl salt and recrystallized from EtOAc/MeOH to give
30 **122** as a white solid (m.p. 275-276°C).

EXAMPLE 76: 4-[6-(Dipropylamino)-3,5,6,7-tetrahydro-1,3-
dioxocyclopent[f]isoindol- 2(1H)-yl]benzonitrile 123

35 Using procedure 49, 2-(dipropylamino)-2,3-dihydro-1H-indene-5,6-dicarboxylate (**92**, 0.3 g, 1.0 mmol) was treated with 4-aminobenzonitrile (0.47 g, 4.0 mmol).

Purification on silica gel, eluting with 3:1 hexane/acetone, afforded a solid that was converted to an HCl salt and recrystallized from EtOAc/ethanol to give **123** as a white solid (m.p. 250-251°C).

5 EXAMPLE 77: 6-(Dipropylamino)-6,7-dihydro-2-(phenylmethyl)cyclopent[f]isoindole- 1,3(2H,5H)-dione 124

Using procedure 49, 2-(dipropylamino)-2,3-dihydro-1H-indene-5,6-dicarboxylate (**92**, 0.3 g, 1.0 mmol) was treated with benzylamine (0.44 mL, 4.0 mmol). Purification
10 on silica gel, eluting with 3:1 hexane/acetone, afforded a solid that was converted to an HCl salt and recrystallized from EtOAc/2-propanol to give **124** as a white solid (m.p. 247-248°C).

EXAMPLE 78: 6-(Dipropylamino)-3,5,6,7-tetrahydro-2-
15 (phenylmethyl)cyclopent[f]isoindol- 1(2H)-one 125

Using procedure 47, 6-(Dipropylamino)-6,7-dihydro-2-(phenylmethyl)cyclopent[f]isoindole- 1,3(2H,5H)-dione (**124**, 0.41 g, 1.0 mmol) was reduced with Zinc dust (0.65 g, 10.0 mmol) in glacial HOAc (20 mL). Purification on
20 silica gel, eluting with 3:1 hexane/acetone gave an oil that was converted to an HCl salt and recrystallized from EtOAc/MeOH to give **125** as a white solid (m.p. 235-236°C).

EXAMPLE 79: 6-(Dipropylamino)-3,5,6,7-tetrahydro-2-
25 methylcyclopent[f]isoindol-1(2H)-one 126

Using procedure 47, the 6-(dipropylamino)-6,7-dihydro-2-methylcyclopent[f]isoindole-1,3(2H,5H)- dione (**120**, 0.13 g, 0.4 mmol) was reduced with Zinc dust (0.26 g, 4.0 mmol) in glacial HOAc (10 mL). Purification via crystallization from EtOAc/MeOH
30 gave an off-white solid that was converted to an HCl salt and recrystallized from EtOAc/MeOH to give **126** as a white solid (m.p. 242-243°C).

EXAMPLE 80: 6-(Dipropylamino)-3,5,6,7-tetrahydro-2-
phenylcyclopent[f]isoindol-1(2H)-one 127

35 Using procedure 47, 6-(dipropylamino)-6,7-dihydro-2-phenylcyclopent[f]isoindole-

1,3(2H,5H)-dione (**121**, 0.09 g, 0.23 mmol) was reduced with Zinc dust (0.15 g, 2.3 mmol) in glacial HOAc (5 mL). Purification on silica gel, eluting with 3:1 hexane/acetone gave an oil that was converted to an HCl salt and recrystallized from EtOAc/MeOH to give **127** as a white solid (m.p. 248-249°C).

5

EXAMPLE 81: 6-(Dipropylamino)-3,5,6,7-tetrahydro-2-[[4-(trifluoromethoxy)phenyl]methyl]cyclopent[f]isoindol-1(2H)-one 128

Using procedure 47, 6-(dipropylamino)-6,7-dihydro-2-[[4-(trifluoromethoxy)phenyl]methyl]cyclopent[f]isoindole-1,3(2H,5H)-dione (**107**, 0.17 g, 0.37 mmol) was reduced with Zinc dust (0.24 g, 3.7 mmol) in glacial HOAc (10 mL). The resulting solid was converted to an HCl salt and recrystallized from EtOAc/MeOH to give **128** as a white solid (m.p. 210-211°C).

EXAMPLE 82: 2-[(4-Chlorophenyl)methyl]-6-(dipropylamino)-3,5,6,7-tetrahydrocyclopent[f]isoindol-1(2H)-one 129

Using procedure 47, 2-[(4-Chlorophenyl)methyl]-6-(dipropylamino)-6,7-dihydrocyclopent[f]isoindole-1,3(2H,5H)-dione (**102**, 0.59 g, 1.43 mmol) was reduced with Zinc dust (0.94 g, 14.3 mmol) in glacial HOAc (100 mL). Purification using silica gel, eluting with 4:1 hexane/acetone, afforded an oil that was converted to an HCl salt and recrystallized from EtOAc/MeOH to give **129** as a white solid (m.p. 233-234°C).

EXAMPLE 83: 6-(Dipropylamino)-3,5,6,7-tetrahydro-2-[(4-methoxyphenyl)methyl]cyclopent[f]isoindol-1(2H)-one 130

Using procedure 47, 6-(dipropylamino)-6,7-dihydro-2-[(4-methoxyphenyl)methyl]cyclopent[f]isoindole-1,3(2H,5H)-dione (**105**, 0.27 g, 0.67 mmol) was reduced with Zinc dust (0.44 g, 6.7 mmol) in glacial HOAc (20 mL). Purification using silica gel, eluting with 8:1 CH₂Cl₂/acetone, afforded an oil that was converted to an HCl salt and recrystallized from EtOAc/MeOH to give **130** as a white solid (m.p. 227-228°C).

EXAMPLE 84: 6-(Dipropylamino)-3,5,6,7-tetrahydro-2-[[4-(trifluoromethyl)phenyl]methyl]cyclopent[f]isoindol-1(2H)-one 131

Using procedure 47, 6-(dipropylamino)-6,7-dihydro-2-[[4-(trifluoromethyl)phenyl)methyl] cyclopent[*f*]isoindole-1,3(2*H*,5*H*)-dione (**108**, 0.44 g, 1 mmol) was reduced with Zinc dust (1.2 g, 18.4 mmol) in glacial HOAc (20 mL). Purification using silica gel, eluting with 9:1 CH₂Cl₂/MeOH, afforded an oil that was converted to an HCl salt and recrystallized from methylene chloride/acetone to give **132** as a white solid (m.p. 190-192°C).

EXAMPLE 85: 6-(Dipropylamino)-2-[(4-fluorophenyl)methyl]- 3,5,6,7-tetrahydrocyclopent[*f*]isoindol-1(2*H*)-one 132

10

Using procedure 47, 6-(dipropylamino)-2-[(4-fluorophenyl)methyl]-6,7-dihydrocyclopent[*f*]isoindole-1,3(2*H*,5*H*)-dione (**101**, 0.56 g, 1.43 mmol) was reduced with Zinc dust (0.94 g, 14.3 mmol) in glacial HOAc (20 mL). Purification using silica gel, eluting with 9:1 CH₂Cl₂/MeOH, afforded an oil that was converted to an HCl salt and recrystallized from EtOAc/MeOH to give **132** as a white solid (m.p. 227-228°C).

15

EXAMPLE 86: Procedure 50. 4-[[6-(Dipropylamino)-3,5,6,7-tetrahydro-1-oxocyclopent[*f*]isoindol- 2(1*H*)-yl)methyl]benzonitrile 133

20

To a slurry of washed NaH (0.05 g, 1.32 mmol) in DMF (5 mL) was added a slurry of 6-(Dipropylamino)-3,5,6,7-tetrahydrocyclopent[*f*]isoindol-1(2*H*)-one (**94**, 0.30 g, 1.10 mmol) in DMF (10 mL). The slurry was heated to 84°C and after 40 min, was treated with a solution of alpha-bromo-p-tolunitrile (0.43 g, 2.20 mmol) in DMF (10 mL). After 24 h, the reaction was quenched with H₂O and extracted with CH₂Cl₂. The organic layers were washed with brine, dried (MgSO₄), and concentrated on hi-vac. The residue was purified on silica gel, eluting with CH₂Cl₂/MeOH to give an oil that was converted to an HCl salt and recrystallized to afford **133** as a white solid (m.p. 141-145°C).

25

30

EXAMPLE 87: Procedure 51: 7-(Dipropylamino)-2,3,7,8-tetrahydro-1*H*-cyclopenta[*g*]phthalazine- 1,4(6*H*)-dione 134

A mixture of 2-(dipropylamino)-2,3-dihydro-1*H*-indene-5,6-dicarboxylate (**92**, 0.17 g, 0.5 mmol) and hydrazine hydrochloride (0.05 g, 0.7 mmol) in glacial HOAc (10 mL) was refluxed at 125 °C for 4 h. The reaction was cooled, concentrated, and

35

converted to an HCl salt. The resulting solid was recrystallized from EtOAc/MeOH to give a white solid. This white solid was further purified via reverse phase chromatography eluting with H₂O/MeOH (95:5). The resulting product was converted to an HCl salt and recrystallized from hot MeOH to give **134** as a white solid (m.p. > 300°C).

EXAMPLE 88: 7-(Dipropylamino)-2,3,7,8-tetrahydro-2-(phenylmethyl)- 1H-cyclopenta[g]phthalazine-1,4(6H)-dione 135

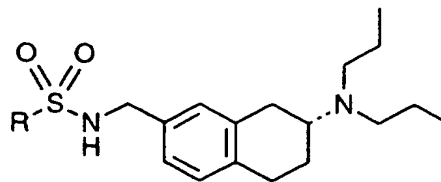
10

Using procedure 51, 2-(dipropylamino)-2,3-dihydro-1H-indene-5,6-dicarboxylate (**92**, 0.349 g, 1 mmol) was treated with benzylhydrazine dihydrochloride (0.27 g, 1.4 mmol) in HOAc (20 mL). Purification using silica gel, eluting with 19:1 CH₂Cl₂/MeOH, afforded a solid that was converted to an HCl salt and recrystallized from EtOAc/MeOH to give **135** as a white solid (m.p. 219-220°C).

15

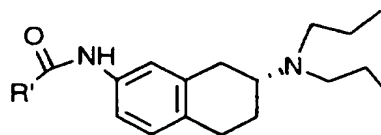
Following are Schemes 1-3, as described above. In Scheme 1 the compounds of the invention are structurally represented as follows:

	<u>R</u>	<u>Compound #</u>
5	CH ₃	10
	4-CN-Ph	11
	4-Cl-Ph	12
	3-NO ₂ -Ph	13
	3-CN-Ph	14
10	4-(1-methyl-1H-imidazole)	15



In Scheme 2 the compounds of the invention are structurally represented as follows:

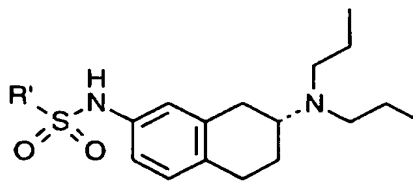
	<u>R'</u>	<u>Compound #</u>
15	4-Cl-Ph	17
	4-CN-Ph	18



20

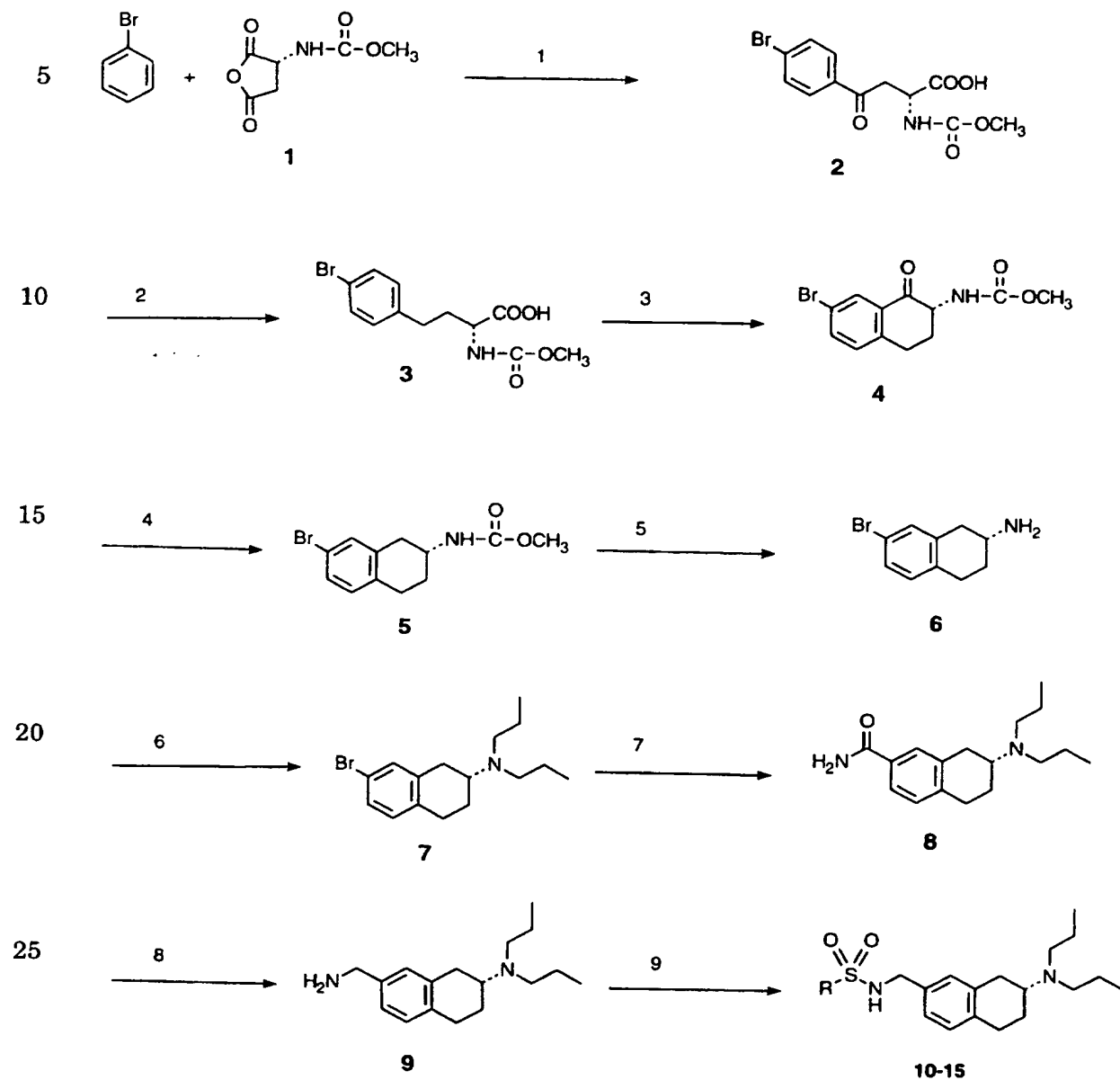
and

	<u>R'</u>	<u>Compound #</u>
25	4-Cl-Ph	20
	4-CN-Ph	21

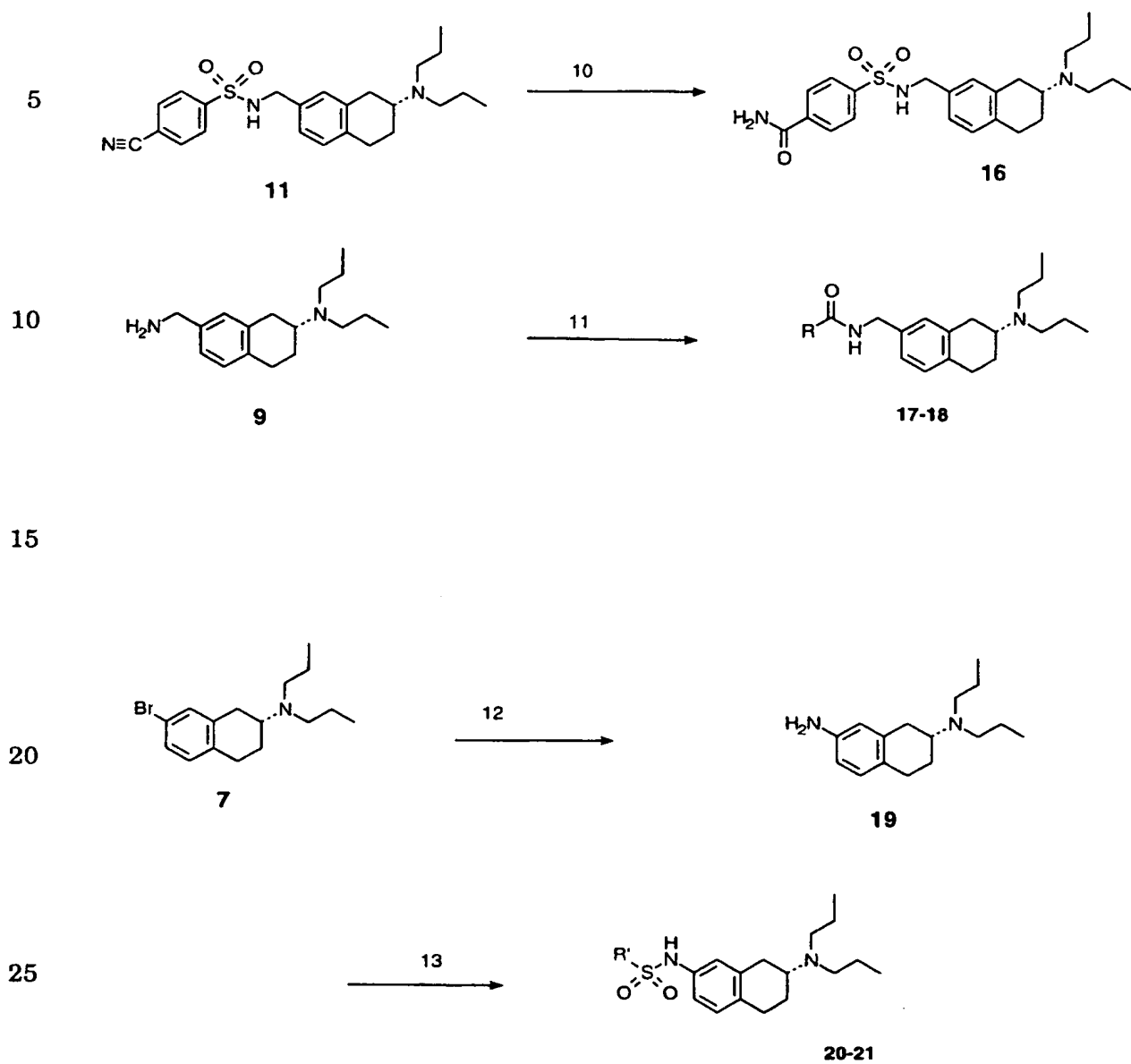


30

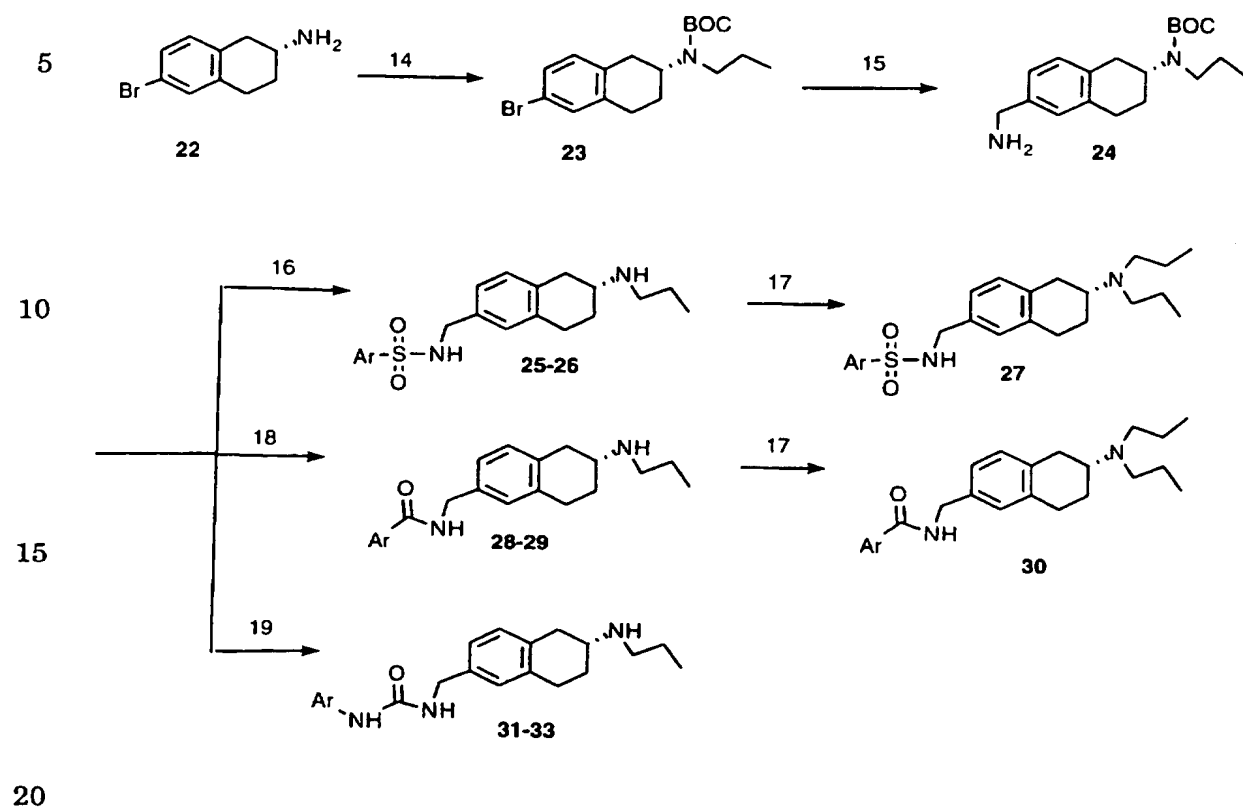
Schem 1



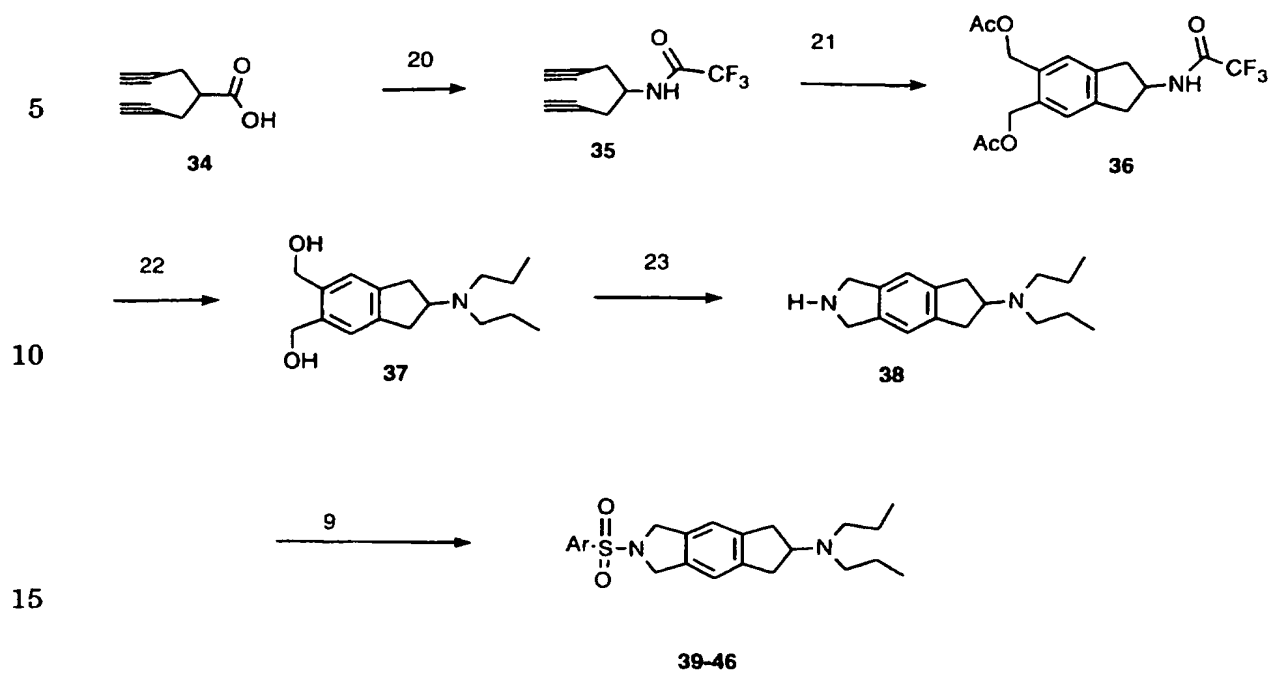
Scheme 2



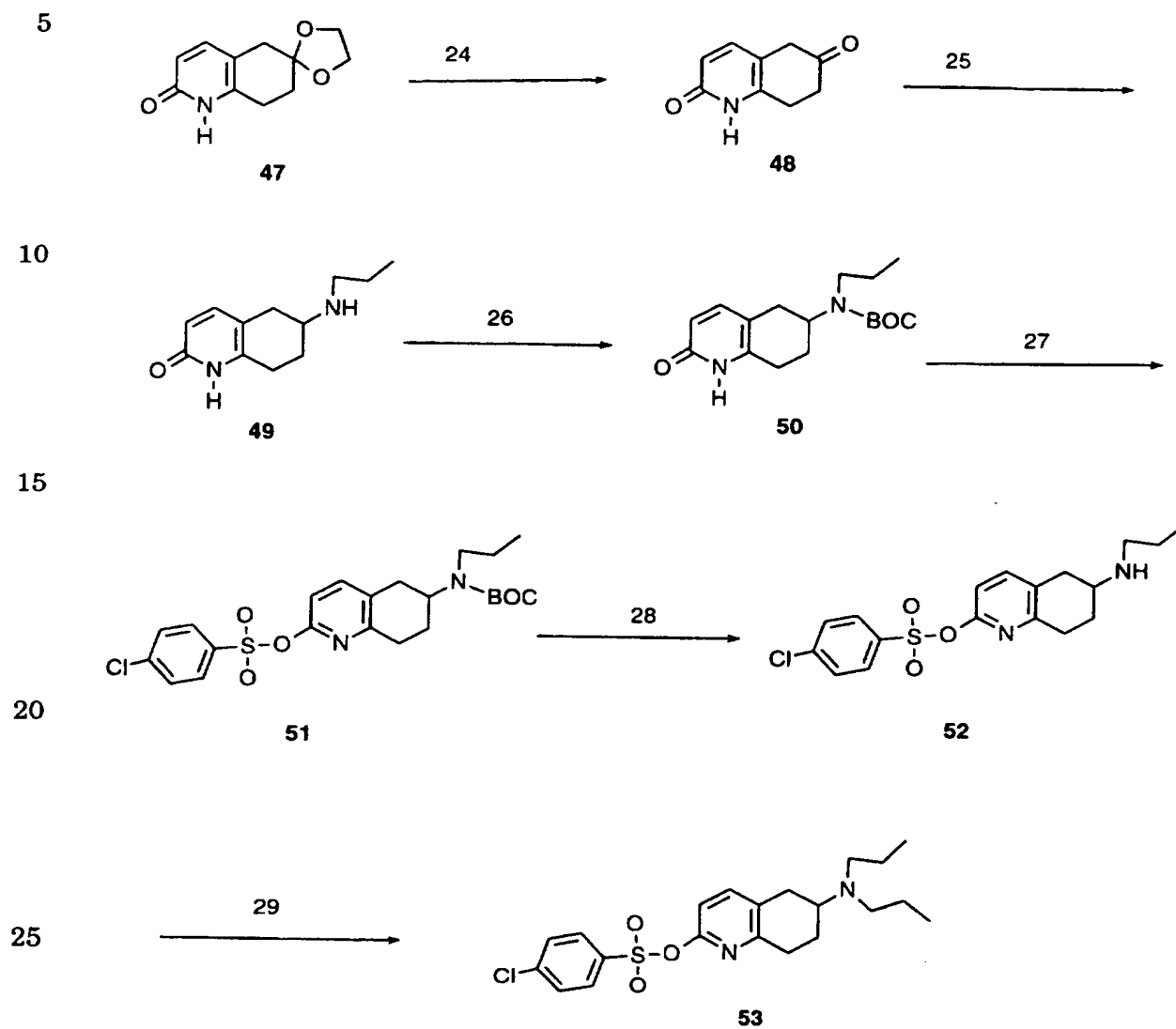
Scheme 3



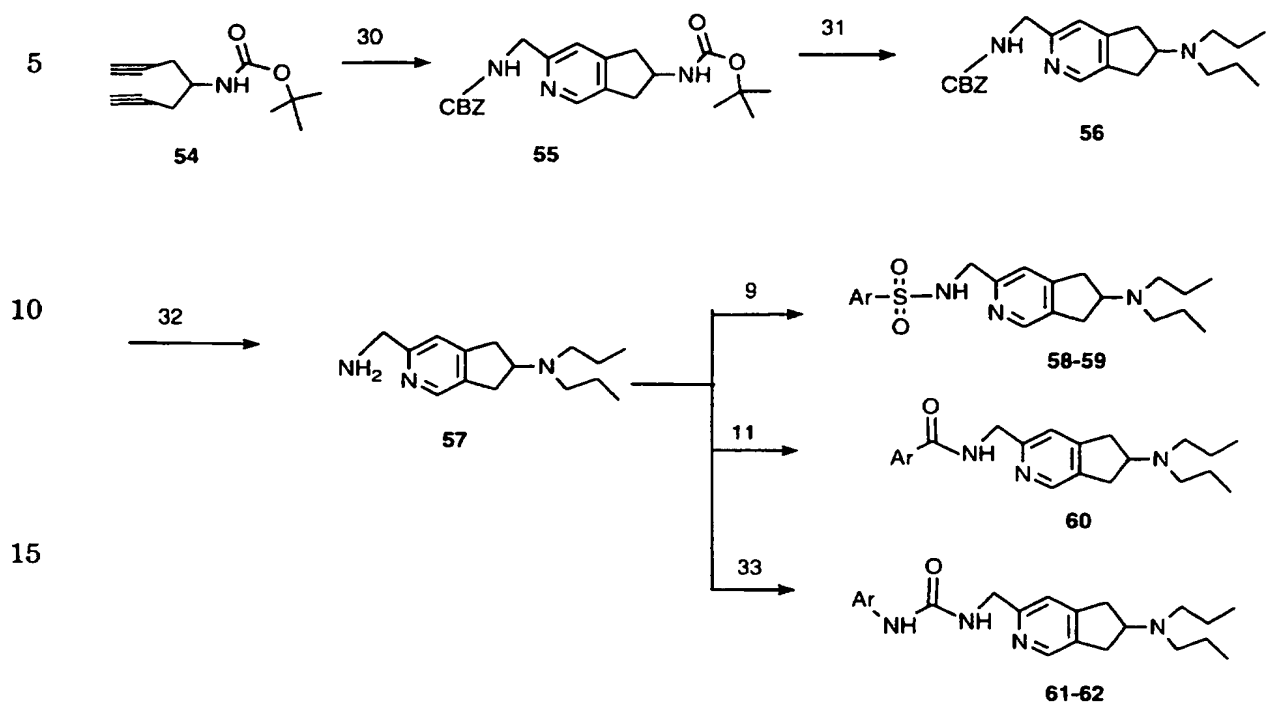
Scheme 4



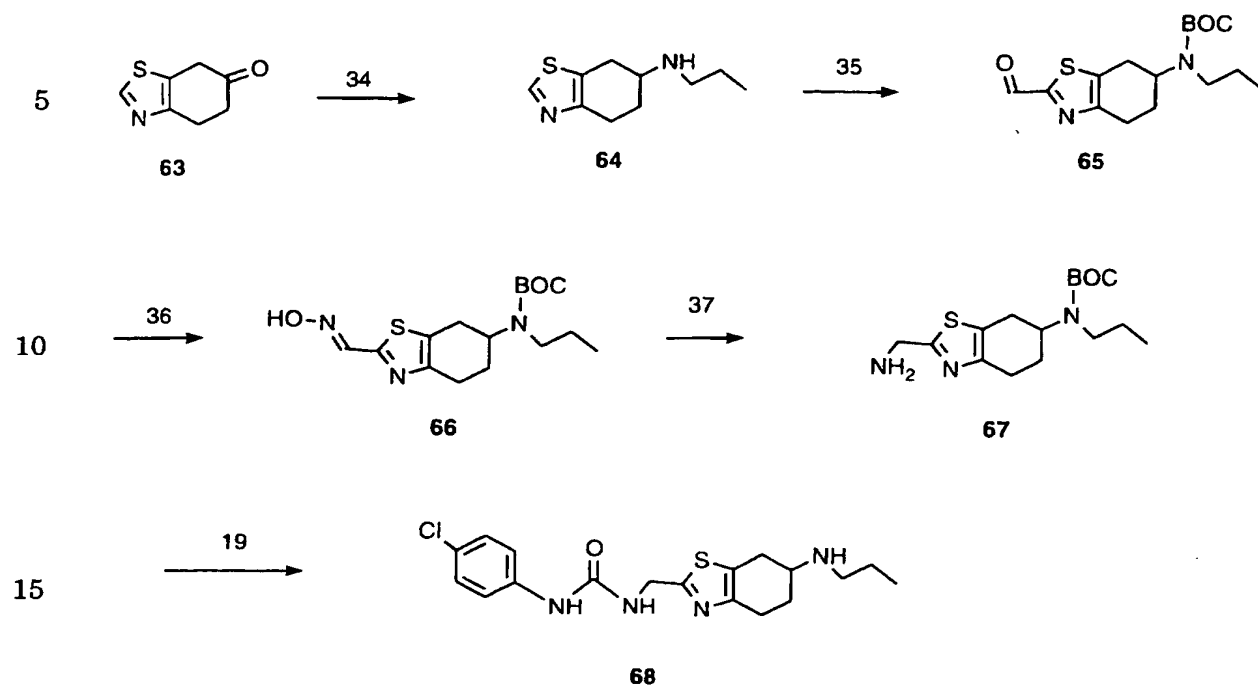
Scheme 5



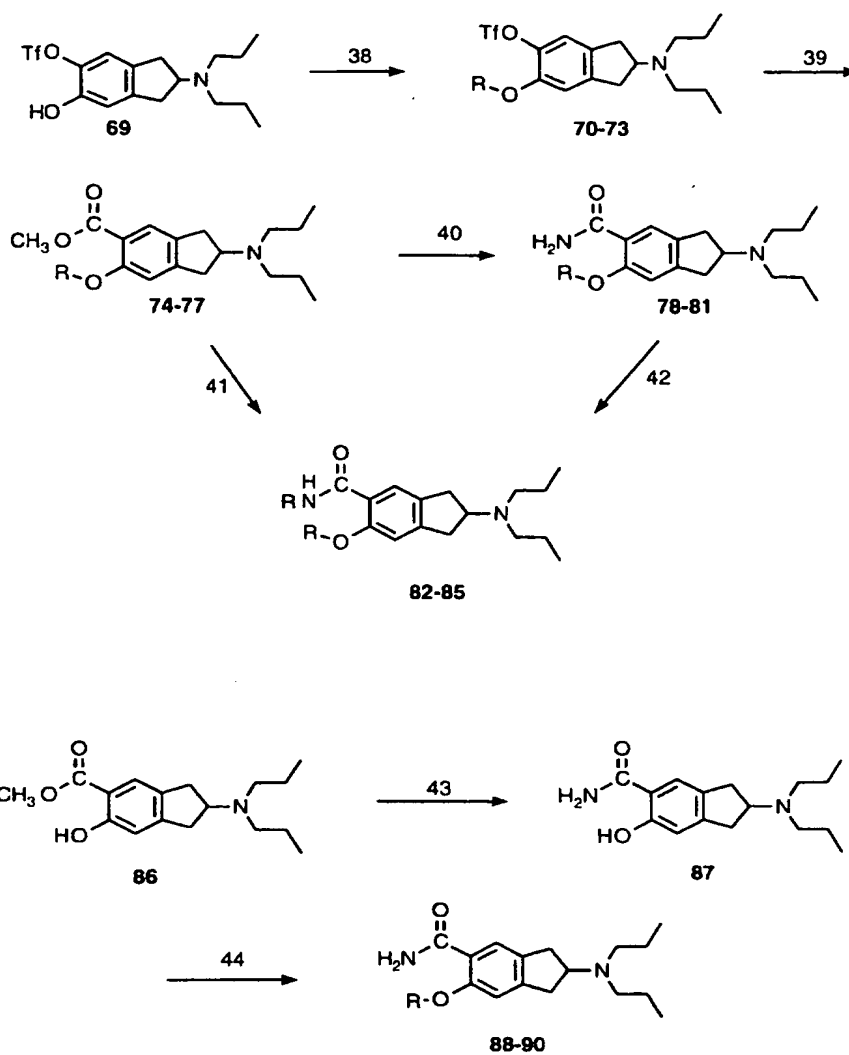
Schem 6



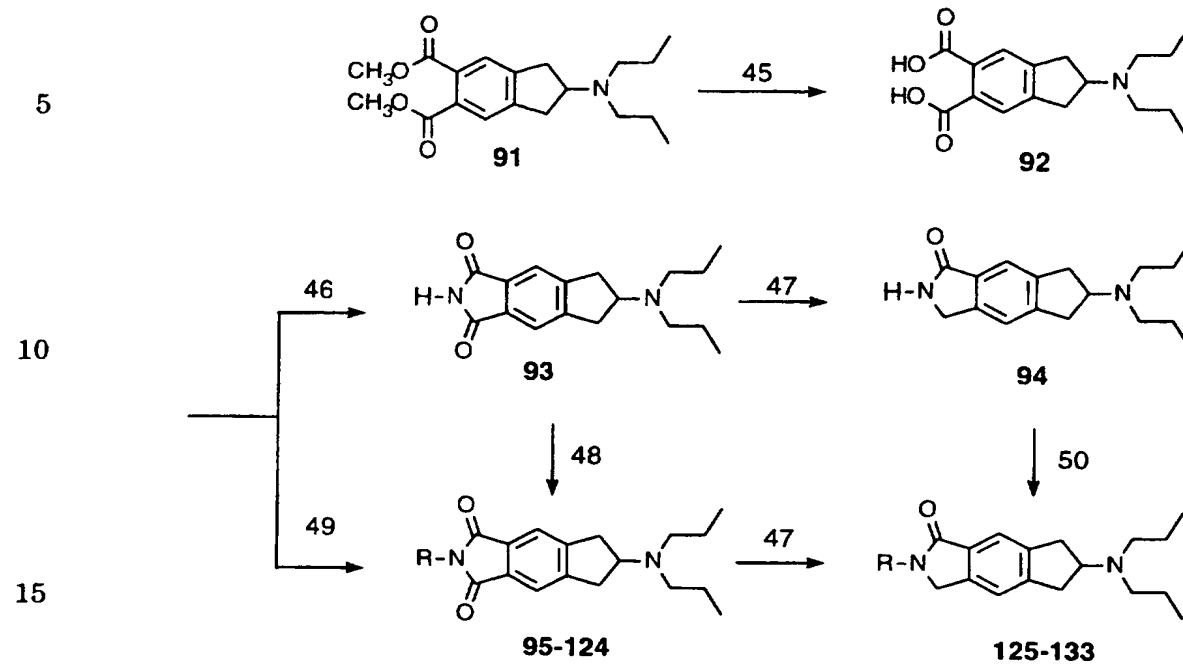
Scheme 7



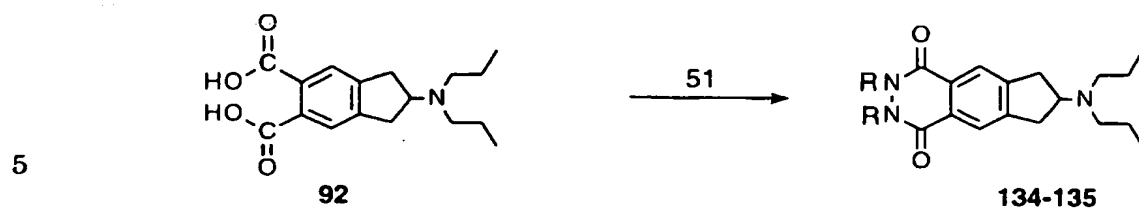
Scheme 8



Scheme 9



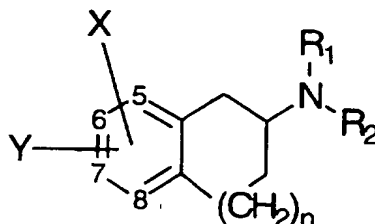
Scheme 10



10

WHAT IS CLAIMED:

1. A compound of structural Formula I or its pharmaceutically acceptable salts:



10 where X and Y are at the 5, 6, or 7 position wherein

- i) n is 1 then X is $(\text{CH}_2)_m\text{CONR}_4\text{R}_5$, $(\text{CH}_2)_m\text{SO}_2\text{R}_3$, $(\text{CH}_2)_m\text{SO}_2\text{NR}_4\text{R}_5$, $(\text{CH}_2)_m\text{NR}_4\text{CONHR}_5$, $(\text{CH}_2)_m\text{NHSO}_2\text{R}_3$, $(\text{CH}_2)_m\text{NHCOR}_3$, or $\text{C}(\text{O})\text{R}_4$ (where m is 0 or 1, except that where m is 0, then Y is not hydrogen or halogen); and
- 15 Y is R_4 , $(\text{CH}_2)_p\text{CONR}_4\text{R}_5$, $(\text{CH}_2)_p\text{CN}$, $(\text{CH}_2)_p\text{SO}_2\text{NR}_4\text{R}_5$, OR_6 , $(\text{CH}_2)_p\text{SO}_2\text{R}_3$, $(\text{CH}_2)_p\text{NHSO}_2\text{R}_3$, halogen or $(\text{CH}_2)_p\text{NHCOR}_3$ (where p is 0 or 1);
- ii) n is 0 or 1 then X and Y are in *ortho*-positions relative to each other and are jointly:
- 20 a) $-\text{C}(\text{O})\text{NR}_{10}\text{C}(\text{O})-$,
 b) $-\text{C}(\text{O})\text{NR}_4(\text{CH}_2)_x\text{NR}_{10}\text{C}(\text{O})-$ (where x is 0 or 1),
 c) $-\text{CH}_2\text{NR}_{10}\text{C}(\text{O})-$,
 d) $-(\text{CH}_2)_2\text{NR}_{10}\text{C}(\text{O})-$,
 e) $-\text{CH}_2\text{C}(\text{O})\text{NR}_{10}-$,
 25 f) $-\text{N}(\text{R}_3)-\text{C}(\text{O})-\text{N}(\text{R}_3)-$,
 g) $-\text{N}(\text{R}_3)-\text{C}(\text{O})-\text{O}-$,
 h) $-\text{N}=\text{C}(\text{R}_7)-\text{N}(\text{R}_3)-$, or
 j) $-\text{CH}_2\text{N}(\text{R}_8)\text{CH}_2-$; or
- iii) n is 0 and Y is OR_9 then X is
- 30 $(\text{CH}_2)_m\text{CONR}_4\text{R}_5$, $(\text{CH}_2)_m\text{SO}_2\text{NR}_4\text{R}_5$, $(\text{CH}_2)_m\text{NR}_4\text{CONHR}_5$, $(\text{CH}_2)_m\text{SO}_2\text{R}_3$, $(\text{CH}_2)_m\text{NHSO}_2\text{R}_3$ or $(\text{CH}_2)_m\text{NHCOR}_3$, $\text{C}(\text{O})\text{R}_4$ (where m is 0 or 1);
- R_1 and R_2 are independently H, C_1 - C_8 alkyl or C_1 - C_8 alkylAryl;
 R_3 is C_1 - C_8 alkyl, C_1 - C_6 alkylAryl or Aryl;
 R_4 and R_5 are independently H, C_1 - C_8 alkyl, C_1 - C_6 alkylAryl or Aryl;
 35 R_6 is H, C_1 - C_8 alkyl, C_1 - C_6 alkylAryl, Aryl SO_2CF_3 , SO_2 - C_1 - C_8 alkyl, SO_2 - C_1 - C_6 alkylAryl, SO_2 -Aryl;

R_7 is hydrogen, $\text{CON}(R_4)_2$, $\text{SO}_2\text{N}(R_4)_2$ or SO_2R_4 ;

R_8 is C_1 - C_8 alkyl, C_1 - C_6 alkylAryl, Aryl, $\text{CON}(R_4)_2$, COR_4 , $\text{SO}_2\text{N}(R_4)_2$ or SO_2R_4 (provided in each case R_4 is not hydrogen);

R_9 is C_2 - C_8 alkyl (optionally substituted with 1 to 3 halogens), C_1 - C_6 alkylAryl, or Aryl; and

R_{10} is H, C_1 - C_8 alkyl, C_1 - C_6 alkylAryl, Aryl or $(\text{CH}_2)_{0-6}\text{SO}_2\text{Aryl}$.

2. The compound of Claim 1 wherein n is 1.

10 3. The compound of Claim 1 wherein R_1 and R_2 are independently H or C_{1-6} alkyl.

4. The compound of Claim 3 wherein R_1 and R_2 are both propyl.

15 5. The compound of Claim 1 wherein Y is hydrogen.

6. The compound of Claim 1 wherein X is $(\text{CH}_2)_m\text{NHSO}_2R_3$.

7. The compound of Claim 6 wherein R_3 is phenyl optionally substituted with CN, Cl, NO_2 or methyl.

8. The compound of Claim 1 where n is 0 and X and Y are jointly

a) $-\text{C}(\text{O})\text{NR}_{10}\text{C}(\text{O})-$,

b) $-\text{C}(\text{O})\text{NR}_4(\text{CH}_2)_x\text{NR}_{10}\text{C}(\text{O})-$ (where x is 0 or 1),

25 c) $-\text{CH}_2\text{NR}_{10}\text{C}(\text{O})-$ or

j) $-\text{CH}_2\text{N}(R_8)\text{CH}_2-$.

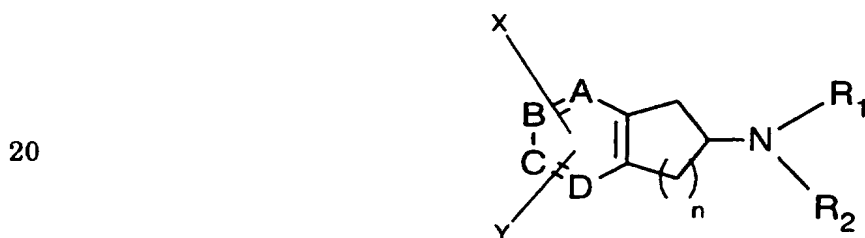
9. The compound of Claim 8 wherein X and Y are jointly $-\text{C}(\text{O})\text{NR}_{10}\text{C}(\text{O})-$, where R_{10} is hydrogen, CH_2Aryl or C_1 - C_3 alkylphenyl (optionally substituted with F, Cl, OCH_3 , OCF_3 , CF_3 , CO_2CH_3 or CN).

10. The compound of Claim 9 wherein said Aryl is benzotriazole, thiophenyl or phenyl.

35 11. The compound of Claim 8 wherein X and Y are jointly -

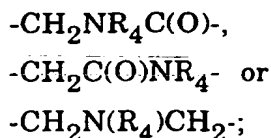
$\text{C}(\text{O})\text{NR}_4(\text{CH}_2)_x\text{NR}_{10}\text{C}(\text{O})-$, where x is 0, R_4 is hydrogen and R_{10} is hydrogen.

12. The compound of Claim 8 wherein X and Y are jointly $-\text{CH}_2\text{NR}_{10}\text{C(O)}-$, where R_{10} is hydrogen or CH_2phenyl (optionally substituted with a F, Cl, OCH_3 , OCF_3 , CF_3 , or CN).
13. The compound of Claim 8 wherein X and Y are jointly $-\text{CH}_2\text{N(R}_8\text{)CH}_2-$, where R_8 is $\text{SO}_2\text{benzoxadiazole}$, $\text{SO}_2\text{oxazolyl}$, $\text{SO}_2\text{thiophenyl}$ or SO_2phenyl (all of which can be optionally substituted with 1 or 2 Cl, CH_3 or CN).
14. The compound of Claim 1 where n is 0 and Y is OR_9 where R_9 is $\text{C}_2 - \text{C}_8$ alkyl (optionally substituted with 1 to 3 halogens); and
X is $(\text{CH}_2)_m\text{CONR}_4\text{R}_5$ where R_4 and R_5 are independently H, methyl or ethyl.
15. The compound of Claim 14 which is 2-(Dipropylamino)-6-ethoxy-2,3-dihydro-1H-indene-5-carboxamide.
16. A compound of structural Formula II or its pharmaceutically acceptable salts:



- where one of A, B, C or D is nitrogen and the remaining positions are CH;
n is 1 or 2;
X and Y are:

- i) substituted at positions A, B, C, or D wherein
X is $(\text{CH}_2)_m\text{CONR}_4\text{R}_5$, $(\text{CH}_2)_m\text{CN}$, $(\text{CH}_2)_m\text{SO}_2\text{NR}_4\text{R}_5$, OSO_2R_3 ,
 $(\text{CH}_2)_m\text{NR}_4\text{CONHR}_5$, $(\text{CH}_2)_m\text{SO}_2\text{R}_3$, $(\text{CH}_2)_m\text{NHSO}_2\text{R}_3$ or
30 $(\text{CH}_2)_m\text{NHCOR}_3$, C(O)R_4 (where m is 0 or 1, except that where m is 0, Y is not hydrogen or halogen); and
Y is R_4 , $(\text{CH}_2)_p\text{CONR}_4\text{R}_5$, $(\text{CH}_2)_p\text{CN}$, $(\text{CH}_2)_p\text{SO}_2\text{NR}_4\text{R}_5$, OR_6 ,
 OSO_2R_3 , $(\text{CH}_2)_p\text{SO}_2\text{R}_3$, $(\text{CH}_2)_p\text{NHSO}_2\text{R}_3$, halogen or $(\text{CH}_2)_p\text{NHCOR}_3$
(where p is 0 or 1); or
- ii) jointly in an *ortho*-positions relative to each other and are:
 $-\text{C(O)NR}_4\text{C(O)}-$,



R_1 and R_2 are independently H, C_1 - C_8 alkyl or C_1 - C_8 alkylAryl;

5 R_3 is C_1 - C_8 alkyl, C_1 - C_6 alkylAryl or Aryl;

R_4 and R_5 are independently H, C_1 - C_8 alkyl, C_1 - C_6 alkylAryl or Aryl; and

R_6 is H, SO_2CF_3 , SO_2CH_3 , SO_2Aryl , C_1 - C_8 alkyl, C_1 - C_6 alkylAryl or Aryl.

17. The compound of Claim 16 wherein n is 1.

10

18. The compound of Claim 16 wherein R_1 and R_2 are independently hydrogen or

C_{1-6} alkyl .

15 19. The compound of Claim 18 wherein R_1 and R_2 are both propyl.

20. The compound of Claim 16 wherein position "C" is N.

21. The compound of Claim 20 wherein said "B" position is substituted with

20 $\text{CH}_2\text{NR}_4\text{CONHR}_5$, $\text{CH}_2\text{SO}_2\text{R}_3$ or $\text{CH}_2\text{NHCOR}_3$.

22. The compound of Claim 16 wherein n is 2.

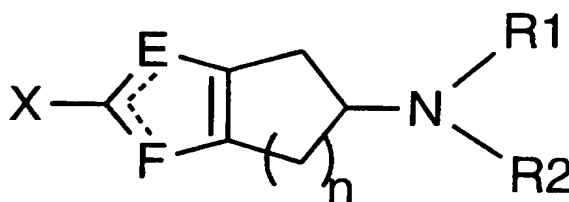
23. The compound of Claim 16 wherein position "D" is N.

25

24. The compound of Claim 23 wherein position "C" is substituted with OSO_2R_3 and R_3 is phenyl (optionally substituted with 1 or 2 Cl, CH_3 or CN).

25. A compound of structural Formula III or its pharmaceutically acceptable salts:

5



wherein one of E or F is N and the other is S;

n is 1 or 2;

R₁ and R₂ are independently H, C₁ - C₈ alkyl or C₁ - C₈ alkylAryl;

- 10 X is (CH₂)_mCONR₄R₅, (CH₂)_mCN, (CH₂)_mSO₂NR₄R₅, (CH₂)_mNR₄CONHR₅, (CH₂)_mSO₂R₃, (CH₂)_mNHSO₂R₃, (CH₂)NHCOR₃ or C(O)R₄ (where, m is 0 or 1);
R₃ is C₁ - C₈ alkyl, C₁ - C₆ alkylAryl or Aryl;
R₄ and R₅ are independently H, C₁ - C₈ alkyl, C₁ - C₆ alkylAryl or Aryl.

- 15 26. The compound of Claim 25, wherein "F" is N and "E" is S.

27. The compound of Claim 25, wherein R₁ and R₂ are independently hydrogen or C₁ - C₈ alkyl.

- 20 28. The compound of Claim 25, wherein X is (CH₂)_mNR₄CONHR₅.

29. The compound of Claim 28, wherein m is 1, R₄ is hydrogen and R₅ is Aryl.

- 25 30. The compound of Claim 29, wherein Aryl is phenyl (optionally substituted with a chlorine atom).

31. A method for treating central nervous system disorders associated with dopamine D3 receptor activity comprising:

- 30 administering to a patient in need thereof a therapeutically effective amount of a compound of Formula I of Claim 1.

32. A method for treating central nervous system disorders associated with dopamine D3 receptor activity comprising:

- 35 administering to a patient in need thereof a therapeutically effective amount of a compound Formula II of Claim 16.

33. A method for treating central nervous system disorders associated with dopamine $\overline{D}3$ receptor activity comprising:

administering to a patient in need thereof a therapeutically effective amount of a compound Formula III of Claim 25.

5

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/07650

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6	C07C311/05	C07C311/18	C07D233/84	C07C233/78	C07C255/57
	C07D261/10	C07C235/84	C07C275/30	C07C275/38	C07D209/70
	A61K31/18	A61K31/415	A61K31/165	A61K31/275	A61K31/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 38, no. 12, 1995, WASHINGTON US, pages 2202-16, XP002036487 P. STJERNLÖF ET AL.: "Structure-activity relationship in the 8-amino-6,7,8,9-tetrahydro-3H-Benz[e]indol ring system. 1. Effects of substituents in the aromatic system on serotonin and dopamine receptor subtypes" see page 2207, table 1, compound 32 see page 2213, left-hand column, line 27 - line 45 --- -/--	1-4, 31-33

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

30 July 1997

Date of mailing of the international search report

11.08.97

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Seufert, G

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/07650

A. CLASSIFICATION OF SUBJECT MATTER IPC 6 A61K31/17 A61K31/40		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols)		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BIOORG. & MED. CHEM. LETT., vol. 6, no. 4, 1996, pages 403-8, XP002036488 P. J. MURRAY ET AL.: "Novel 6-substituted 2-aminotetralins with potent and selective affinity for the dopamine D3 receptor" cited in the application see page 406, table 3, compounds 25-27 29 see page 408, scheme 4 see page 405, line 7 - line 16 ---	1-5, 31-33
X	WO 94 21608 A (UPJOHN CO ;ANDERSSON BENGT RONNY (SE); CARLSSON PER ARVID EMIL (SE) 29 September 1994 see claim 1; example 35 see page 32, line 10 - line 22 --- <div style="text-align: center;">-/--</div>	1-5
<div style="display: flex; justify-content: space-between;"> <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input type="checkbox"/> Patent family members are listed in annex. </div>		
* Special categories of cited documents :		
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>* "A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>* "E" earlier document but published on or after the international filing date</p> <p>* "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>* "O" document referring to an oral disclosure, use, exhibition or other means</p> <p>* "P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>* "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>* "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>* "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>* "&" document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search	Date of mailing of the international search report	
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Authorized officer	

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/07650

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 968 679 A (JUNGE BODO ET AL) 6 November 1990 cited in the application see claim 1; examples 14,15,18-20 ---	1-6
X	US 4 448 990 A (BACH NICHOLAS J ET AL) 15 May 1984 see claims 1,2,4-8; examples 3,7; table 1 ---	1-4
X	EP 0 074 903 A (SYNTHELABO) 23 March 1983 see table I, compounds 2d), 7, 8, 22 see claim 1 ---	1-4
X	DE 27 52 659 A (SANDOZ AG) 8 June 1978 see table II, compounds 29, 33, 34 see claim 1 ---	1-3
A	WO 95 04713 A (UPJOHN CO ;HAADSMA SVENSSON SUSANNE R (US); ANDERSSON BENGT R (SE)) 16 February 1995 cited in the application see claims; examples ---	1-15, 31-33
A	EP 0 186 087 A (THOMAE GMBH DR K) 2 July 1986 see claims ---	25
P,X	WO 96 30333 A (SMITHKLINE BEECHAM PLC ;STEMP GEOFFREY (GB); JOHNSON CHRISTOPHER N) 3 October 1996 see page 23, line 30 - line 33 -----	1-3,5

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 97/07650

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 31-33
is(are) directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/07650

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9421608 A	29-09-94	AU 679053 B AU 6408694 A CA 2157586 A EP 0690843 A JP 8508251 T NZ 263403 A US 5639778 A	19-06-97 11-10-94 29-09-94 10-01-96 03-09-96 28-10-96 17-06-97
US 4968679 A	06-11-90	DE 3719924 A AU 613884 B AU 8302987 A EP 0272534 A JP 63190857 A US 4873262 A US 5047422 A ZA 8709549 A	30-06-88 15-08-91 30-06-88 29-06-88 08-08-88 10-10-89 10-09-91 16-06-88
US 4448990 A	15-05-84	CA 1198122 A EP 0109815 A GB 2130209 A,B JP 59108748 A US 4500545 A	17-12-85 30-05-84 31-05-84 23-06-84 19-02-85
EP 0074903 A	23-03-83	FR 2512814 A AU 551898 B AU 8843082 A CA 1224491 A JP 1354199 C JP 58062141 A JP 61021621 B JP 61165324 A JP 61165323 A US 4442126 A	18-03-83 15-05-86 24-03-83 21-07-87 24-12-86 13-04-83 28-05-86 26-07-86 26-07-86 10-04-84
DE 2752659 A	08-06-78	AT 370409 B AT 366361 B AU 3132877 A CA 1105475 A FR 2373513 A GB 1597140 A	25-03-83 13-04-82 14-06-79 21-07-81 07-07-78 03-09-81

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/07650

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 2752659 A		JP 1407792 C	27-10-87
		JP 53084955 A	26-07-78
		JP 62014540 B	02-04-87
		NL 7713364 A	09-06-78
		SE 7713471 A	08-06-78
		SU 927110 A	07-05-82
		AU 520088 B	14-01-82
		BE 861516 A	05-06-78

WO 9504713 A	16-02-95	AU 7513494 A	28-02-95
		EP 0712387 A	22-05-96
		JP 9501429 T	10-02-97

EP 0186087 A	02-07-86	DE 3447075 A	03-07-86
		DE 3508947 A	18-09-86
		AU 583874 B	11-05-89
		AU 5154485 A	17-07-86
		CA 1263653 A	05-12-89
		CS 9104099 A	16-09-92
		DK 168862 B	27-06-94
		HK 78692 A	23-10-92
		IE 58863 B	17-11-93
		JP 1854941 C	07-07-94
		JP 61155377 A	15-07-86
		US 4843086 A	27-06-89
		US 4886812 A	12-12-89
		US 4731374 A	15-03-88

WO 9630333 A	03-10-96	AU 5147196 A	16-10-96



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/395, 31/40, 31/41, 31/415, 31/425, 31/435, 31/44, 31/445, 31/47, 31/495, 31/535, C07D 205/02, 209/04, 209/14, 209/30, 217/12, 235/02, 233/64, 241/02, 257/04, 265/30, 275/02, 277/02, 277/08, 295/08, 295/26, 401/02, 401/12, 401/14, 413/02, 413/12, 413/14, 417/02, 417/12, 417/14, 487/04, 513/04, C07F 9/02	A1	(11) International Publication Number: WO 98/53814 (43) International Publication Date: 3 December 1998 (03.12.98)												
(21) International Application Number: PCT/US98/10940 (22) International Filing Date: 29 May 1998 (29.05.98) (30) Priority Data: <table border="0" style="width: 100%;"><tr><td style="width: 40%;">60/048,017</td><td style="width: 40%;">29 May 1997 (29.05.97)</td><td style="width: 20%;">US</td></tr><tr><td>9714314.3</td><td>7 July 1997 (07.07.97)</td><td>GB</td></tr><tr><td>60/066,525</td><td>25 November 1997 (25.11.97)</td><td>US</td></tr><tr><td>9800686.9</td><td>14 January 1998 (14.01.98)</td><td>GB</td></tr></table> (71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): DURETTE, Philippe, L. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). HAGMANN, William, K. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). MacCOSS, Malcolm		60/048,017	29 May 1997 (29.05.97)	US	9714314.3	7 July 1997 (07.07.97)	GB	60/066,525	25 November 1997 (25.11.97)	US	9800686.9	14 January 1998 (14.01.98)	GB	<p>[GB/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). MILLS, Sander, G. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). MUMFORD, Richard, A. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). VAN RIPER, Gail, M. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). SCHMIDT, Jack, A. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). KEVIN, Nancy, J. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).</p> (74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (81) Designated States: CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
60/048,017	29 May 1997 (29.05.97)	US												
9714314.3	7 July 1997 (07.07.97)	GB												
60/066,525	25 November 1997 (25.11.97)	US												
9800686.9	14 January 1998 (14.01.98)	GB												
(54) Title: HETEROCYCLIC AMIDE COMPOUNDS AS CELL ADHESION INHIBITORS (57) Abstract Compounds of formula (I) are antagonists of VLA-4 and/or $\alpha_4\beta_7$, and as such are useful in the inhibition or prevention of cell adhesion and cell-adhesion mediated pathologies. These compounds may be formulated into pharmaceutical compositions and are suitable for use in the treatment of asthma, allergies, inflammation, multiple sclerosis, and other inflammatory and autoimmune disorders.														

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav	TM	Turkmenistan
BF	Burkina Faso	GR	Greece		Republic of Macedonia	TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

TITLE OF THE INVENTION**HETEROCYCLIC AMIDE COMPOUNDS AS CELL ADHESION INHIBITORS****SUMMARY OF THE INVENTION**

5 The compounds of the present invention are antagonists of the VLA-4 integrin ("very late antigen-4"; CD49d/CD29; or $\alpha_4\beta_1$) and/or the $\alpha_4\beta_7$ integrin (LPAM-1 and $\alpha_4\beta_p$), thereby blocking the binding of VLA-4 to its various ligands, such as VCAM-1 and regions of fibronectin and/or $\alpha_4\beta_7$ to its various ligands, such as MadCAM-1, VCAM-1 and
10 fibronectin. Thus, these antagonists are useful in inhibiting cell adhesion processes including cell activation, migration, proliferation and differentiation. These antagonists are useful in the treatment, prevention and suppression of diseases mediated by VLA-4 and/or $\alpha_4\beta_7$ binding and cell adhesion and activation, such as multiple sclerosis,
15 asthma, allergic rhinitis, allergic conjunctivitis, inflammatory lung diseases, rheumatoid arthritis, septic arthritis, type I diabetes, organ transplantation, restenosis, autologous bone marrow transplantation, inflammatory sequelae of viral infections, myocarditis, inflammatory bowel disease including ulcerative colitis and Crohn's disease, certain
20 types of toxic and immune-based nephritis, contact dermal hypersensitivity, psoriasis, tumor metastasis, and atherosclerosis.

BACKGROUND OF THE INVENTION

 The present invention relates to heterocyclic amide
25 derivatives which are useful for the inhibition and prevention of leukocyte adhesion and leukocyte adhesion-mediated pathologies. This invention also relates to compositions containing such compounds and methods of treatment using such compounds.

 Many physiological processes require that cells come into
30 close contact with other cells and/or extracellular matrix. Such adhesion events may be required for cell activation, migration, proliferation and differentiation. Cell-cell and cell-matrix interactions are mediated through several families of cell adhesion molecules

(CAMs) including the selectins, integrins, cadherins and immunoglobulins. CAMs play an essential role in both normal and pathophysiological processes. Therefore, the targetting of specific and relevant CAMs in certain disease conditions without interfering with normal cellular functions is essential for an effective and safe therapeutic agent that inhibits cell-cell and cell-matrix interactions.

The integrin superfamily is made up of structurally and functionally related glycoproteins consisting of α and β heterodimeric, transmembrane receptor molecules found in various combinations on nearly every mammalian cell type. (for reviews see: E. C. Butcher, Cell, 67, 1033 (1991); T. A. Springer, Cell, 76, 301 (1994); D. Cox et al., "The Pharmacology of the Integrins." Medicinal Research Rev. 14, 195 (1994) and V. W. Engleman et al., "Cell Adhesion Integrins as Pharmaceutical Targets." in Ann. Repts. in Medicinal Chemistry, Vol. 31, J. A. Bristol, Ed.; Acad. Press, NY, 1996, p. 191).

VLA-4 ("very late antigen-4"; CD49d/CD29; or $\alpha_4\beta_1$) is an integrin expressed on all leukocytes, except platelets and mature neutrophils, including dendritic cells and macrophage-like cells and is a key mediator of the cell-cell and cell-matrix interactions of these cell types (see M. E. Hemler, "VLA Proteins in the Integrin Family: Structures, Functions, and Their Role on Leukocytes." Ann. Rev. Immunol. 8, 365 (1990)). The ligands for VLA-4 include vascular cell adhesion molecule-1 (VCAM-1) and the CS-1 domain of fibronectin (FN). VCAM-1 is a member of the Ig superfamily and is expressed *in vivo* on endothelial cells at sites of inflammation. (See R. Lobb et al. "Vascular Cell Adhesion Molecule 1." in Cellular and Molecular Mechanisms of Inflammation, C. G. Cochrane and M. A. Gimbrone, Eds.; Acad. Press, San Diego, 1993, p. 151.) VCAM-1 is produced by vascular endothelial cells in response to pro-inflammatory cytokines (See A. J. H. Gearing and W. Newman, "Circulating adhesion molecules in disease.", Immunol. Today, 14, 506 (1993). The CS-1 domain is a 25 amino acid sequence that arises by alternative splicing within a region of fibronectin. (For a review, see R. O. Hynes "Fibronectins.", Springer-

Velag, NY, 1990.) A role for VLA-4/CS-1 interactions in inflammatory conditions has been proposed (see M. J. Elices, "The integrin $\alpha_4\beta_1$ (VLA-4) as a therapeutic target" in Cell Adhesion and Human Disease, Ciba Found. Symp., John Wiley & Sons, NY, 1995, p. 79).

5 $\alpha_4\beta_7$ (also referred to as LPAM-1 and $\alpha_4\beta_p$) is an integrin expressed on leukocytes and is a key mediator of leukocyte trafficking and homing in the gastrointestinal tract (see C. M. Parker et al., Proc. Natl. Acad. Sci. USA, **89**, 1924 (1992)). The ligands for $\alpha_4\beta_7$ include mucosal addressing cell adhesion molecule-1 (MadCAM-1) and, upon
10 activation of $\alpha_4\beta_7$, VCAM-1 and fibronectin (Fn). MadCAM-1 is a member of the Ig superfamily and is expressed in vivo on endothelial cells of gut-associated mucosal tissues of the small and large intestine ("Peyer's Patches") and lactating mammary glands. (See M. J. Briskin et al., Nature, **363**, 461 (1993); A. Hamann et al., J. Immunol., **152**, 3282
15 (1994)). MadCAM-1 can be induced in vitro by proinflammatory stimuli (See E. E. Sikorski et al. J. Immunol., **151**, 5239 (1993)). MadCAM-1 is selectively expressed at sites of lymphocyte extravasation and specifically binds to the integrin, $\alpha_4\beta_7$.

 Neutralizing anti- α_4 antibodies or blocking peptides that
20 inhibit the interaction between VLA-4 and/or $\alpha_4\beta_7$ and their ligands have proven efficacious both prophylactically and therapeutically in several animal models of disease, including i) experimental allergic encephalomyelitis, a model of neuronal demyelination resembling multiple sclerosis (for example, see T. Yednock et al., "Prevention of
25 experimental autoimmune encephalomyelitis by antibodies against $\alpha_4\beta_1$ integrin." Nature, **356**, **63** (1993) and E. Keszthelyi et al., "Evidence for a prolonged role of α_4 integrin throughout active experimental allergic encephalomyelitis." Neurology, **47**, 1053 (1996)); ii) bronchial
hyperresponsiveness in sheep and guinea pigs as models for the various
30 phases of asthma (for example, see W. M. Abraham et al., " α_4 -Integrins mediate antigen-induced late bronchial responses and prolonged airway hyperresponsiveness in sheep." J. Clin. Invest. **93**, 776 (1993) and A. A. Y. Milne and P. P. Piper, "Role of VLA-4 integrin in leucocyte

recruitment and bronchial hyperresponsiveness in the guinea-pig." Eur. J. Pharmacol., **282**, 243 (1995)); iii) adjuvant-induced arthritis in rats as a model of inflammatory arthritis (see C. Barbadillo et al., "Anti-VLA-4 mAb prevents adjuvant arthritis in Lewis rats." Arthr. Rheuma. (Suppl.), **36** 95 (1993) and D. Seiffge, "Protective effects of monoclonal antibody to VLA-4 on leukocyte adhesion and course of disease in adjuvant arthritis in rats." J. Rheumatol., **23**, 12 (1996)); iv) adoptive autoimmune diabetes in the NOD mouse (see J. L. Baron et al., "The pathogenesis of adoptive murine autoimmune diabetes requires an interaction between α_4 -integrins and vascular cell adhesion molecule-1.", J. Clin. Invest., **93**, 1700 (1994), A. Jakubowski et al., "Vascular cell adhesion molecule-Ig fusion protein selectively targets activated α_4 -integrin receptors in vivo: Inhibition of autoimmune diabetes in an adoptive transfer model in nonobese diabetic mice." J. Immunol., **155**, 938 (1995), and X. D. Yang et al., "Involvement of beta 7 integrin and mucosal addressin cell adhesion molecule-1 (MadCAM-1) in the development of diabetes in nonobese diabetic mice", Diabetes, **46**, 1542 (1997)); v) cardiac allograft survival in mice as a model of organ transplantation (see M. Isobe et al., "Effect of anti-VCAM-1 and anti-VLA-4 monoclonal antibodies on cardiac allograft survival and response to soluble antigens in mice.", Transplant. Proc., **26**, 867 (1994) and S. Molossi et al., "Blockade of very late antigen-4 integrin binding to fibronectin with connecting segment-1 peptide reduces accelerated coronary arteriopathy in rabbit cardiac allografts." J. Clin. Invest., **95**, 2601 (1995)); vi) spontaneous chronic colitis in cotton-top tamarins which resembles human ulcerative colitis, a form of inflammatory bowel disease (see D. K. Podolsky et al., "Attenuation of colitis in the Cotton-top tamarin by anti- α_4 integrin monoclonal antibody.", J. Clin. Invest., **92**, 372 (1993)); vii) contact hypersensitivity models as a model for skin allergic reactions (see T. A. Ferguson and T. S. Kupper, "Antigen-independent processes in antigen-specific immunity.", J. Immunol., **150**, 1172 (1993) and P. L. Chisholm et al., "Monoclonal antibodies to the integrin α_4 subunit inhibit the murine contact hypersensitivity

response." Eur. J. Immunol., **23**, 682 (1993)); viii) acute neurotoxic nephritis (see M. S. Mulligan et al., "Requirements for leukocyte adhesion molecules in nephrotoxic nephritis.", J. Clin. Invest., **91**, 577 (1993)); ix) tumor metastasis (for examples, see M. Edward, "Integrins and other adhesion molecules involved in melanocytic tumor progression.", Curr. Opin. Oncol., **7**, 185 (1995)); x) experimental autoimmune thyroiditis (see R. W. McMurray et al., "The role of $\alpha 4$ integrin and intercellular adhesion molecule-1 (ICAM-1) in murine experimental autoimmune thyroiditis." Autoimmunity, **23**, 9 (1996); and xi) ischemic tissue damage following arterial occlusion in rats (see F. Squadrito et al., "Leukocyte integrin very late antigen-4/vascular cell adhesion molecule-1 adhesion pathway in splanchnic artery occlusion shock." Eur. J. Pharmacol., **318**, 153 (1996; xii) inhibition of TH2 T-cell cytokine production including IL-4 and IL-5 by VLA-4 antibodies which would attenuate allergic responses (J. Clinical Investigation **100**, 3083 (1997). The primary mechanism of action of such antibodies appears to be the inhibition of lymphocyte and monocyte interactions with CAMs associated with components of the extracellular matrix, thereby limiting leukocyte migration to extravascular sites of injury or inflammation and/or limiting the priming and/or activation of leukocytes.

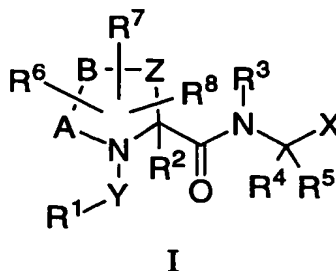
There is additional evidence supporting a possible role for VLA-4 interactions in other diseases, including rheumatoid arthritis; various melanomas, carcinomas, and sarcomas; inflammatory lung disorders; acute respiratory distress syndrome (ARDS); atherosclerotic plaque formation; restenosis; uveitis and circulatory shock (for examples, see A. A. Postigo et al., "The $\alpha 4 \beta 1$ /VCAM-1 adhesion pathway in physiology and disease.", Res. Immunol., **144**, 723 (1994) and J.-X. Gao and A. C. Issekutz, "Expression of VCAM-1 and VLA-4 dependent T-lymphocyte adhesion to dermal fibroblasts stimulated with proinflammatory cytokines." Immunol. **89**, 375 (1996)).

At present, there is a humanized monoclonal antibody (Antegren® Athena Neurosciences/Elan) against VLA-4 in clinical development for the treatment of "flares" associated with multiple

sclerosis and a humanized monoclonal antibody (ACT-1@/LDP-02 LeukoSite) against $\alpha 4\beta 7$ in clinical development for the treatment of inflammatory bowel disease. Several peptidyl antagonists of VLA-4 have been described (D. Y. Jackson et al., "Potent $\alpha 4\beta 1$ peptide antagonists as potential anti-inflammatory agents", J. Med. Chem., **40**, 3359 (1997); H. N. Shroff et al., "Small peptide inhibitors of $\alpha 4\beta 7$ mediated MadCAM-1 adhesion to lymphocytes", Bioorg. Med. Chem. Lett., **6**, 2495 (1996); US 5,510,332, WO97/03094, WO97/02289, WO96/40781, WO96/22966, WO96/20216, WO96/01644, WO96/06108, WO95/15973). There is one report of nonpeptidyl inhibitors of the ligands for $\alpha 4$ -integrins (WO96/31206). There still remains a need for low molecular weight, specific inhibitors of VLA-4- and $\alpha 4\beta 7$ -dependent cell adhesion that have improved pharmacokinetic and pharmacodynamic properties such as oral bioavailability and significant duration of action. Such compounds would prove to be useful for the treatment, prevention or suppression of various pathologies mediated by VLA-4 and $\alpha 4\beta 7$ binding and cell adhesion and activation.

DETAILED DESCRIPTION OF THE INVENTION

One aspect of the present invention provides a method for the treatment of diseases, disorders, conditions or symptoms mediated by cell adhesion in a mammal which comprises administering to said mammal an effective amount of a compound Formula I:



or a pharmaceutically acceptable salt thereof wherein:

- R¹ is
- 1) C₁₋₁₀alkyl,
 - 2) C₂₋₁₀alkenyl,
 - 3) C₂₋₁₀alkynyl,
 - 4) Cy,
 - 5) Cy-C₁₋₁₀alkyl,
 - 6) Cy-C₂₋₁₀alkenyl,
 - 7) Cy-C₂₋₁₀alkynyl,

wherein alkyl, alkenyl, and alkynyl are optionally substituted with one to four substituents independently selected from R^a; and Cy is optionally substituted with one to four substituents independently selected from R^b;

- R² is
- 1) hydrogen,
 - 2) C₁₋₁₀alkyl,
 - 3) C₂₋₁₀alkenyl,
 - 4) C₂₋₁₀alkynyl,
 - 5) aryl,
 - 6) aryl-C₁₋₁₀alkyl,
 - 7) heteroaryl,
 - 8) heteroaryl-C₁₋₁₀alkyl,

wherein alkyl, alkenyl, and alkynyl are optionally substituted with one to four substituents independently selected from R^a; and aryl and heteroaryl optionally substituted with one to four substituents independently selected from R^b;

- R³ is
- 1) hydrogen,
 - 2) C₁₋₁₀ alkyl,
 - 3) Cy, or
 - 4) Cy-C₁₋₁₀ alkyl,

wherein alkyl is optionally substituted with one to four substituents independently selected from R^a; and Cy is optionally substituted with one to four substituents independently selected from R^b;

- R⁴ is
- 1) hydrogen,

- 2) C₁₋₁₀alkyl,
3 C₂₋₁₀alkenyl,
4) C₂₋₁₀alkynyl,
5) Cy,
5 6) Cy-C₁₋₁₀alkyl,
7) Cy-C₂₋₁₀alkenyl,
8) Cy-C₂₋₁₀alkynyl,

wherein alkyl, alkenyl and alkynyl are optionally substituted with one to
four substituents selected from phenyl and R^x, and Cy is optionally
10 substituted with one to four substituents independently selected from R^y;
or
R³, R⁴ and the atoms to which they are attached together form a mono-
or bicyclic ring containing 0-2 additional heteroatoms selected from N, O
and S;

- 15 R⁵ is 1) hydrogen,
2) C₁₋₁₀alkyl,
3) C₂₋₁₀alkenyl,
4) C₂₋₁₀alkynyl,
20 5) aryl,
6) aryl-C₁₋₁₀alkyl,
7) heteroaryl,
8) heteroaryl-C₁₋₁₀alkyl,

wherein alkyl, alkenyl and alkynyl are optionally substituted with one to
25 four substituents selected from R^x, and aryl and heteroaryl are
optionally substituted with one to four substituents independently
selected from R^y; or

R⁴, R⁵ and the carbon to which they are attached form a 3-7 membered
30 mono- or bicyclic ring containing 0-2 heteroatoms selected from N, O and
S;

R⁶, R⁷, and R⁸ are each independently selected from the group consisting of

- 1) a group selected from R^d, and
 - 2) a group selected from R^x; or
- 5 two of R⁶, R⁷, and R⁸ and the atom to which both are attached, or two of R⁶, R⁷, and R⁸ and the two adjacent atoms to which they are attached, together form a 5-7 membered saturated or unsaturated monocyclic ring containing zero to three heteroatoms selected from N, O or S,

- 10 R^a is
- 1) Cy, or
 - 2) a group selected from R^x;
- wherein Cy is optionally substituted with one to four substituents independently selected from R^c;

- 15 R^b is
- 1) a group selected from R^a,
 - 2) C₁₋₁₀ alkyl,
 - 3) C₂₋₁₀ alkenyl,
 - 4) C₂₋₁₀ alkynyl,
 - 5) aryl C₁₋₁₀alkyl,
 - 20 6) heteroaryl C₁₋₁₀ alkyl,
- wherein alkyl, alkenyl, alkynyl, aryl, heteroaryl are optionally substituted with a group independently selected from R^c;

- R^c is
- 1) halogen,
 - 25 2) NO₂,
 - 3) C(O)OR^f,
 - 4) C₁₋₄alkyl,
 - 5) C₁₋₄alkoxy,
 - 6) aryl,
 - 30 7) aryl C₁₋₄alkyl,
 - 8) aryloxy,
 - 9) heteroaryl,
 - 10) NR^fR^g,

- 11) $\text{NR}^f\text{C}(\text{O})\text{R}^g$,
- 12) $\text{NR}^f\text{C}(\text{O})\text{NR}^f\text{R}^g$, or
- 13) CN ;

- 5 R^d and R^e are independently selected from hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, Cy and Cy C_{1-10} alkyl, wherein alkyl, alkenyl, alkynyl and Cy is optionally substituted with one to four substituents independently selected from R^c ; or
- 10 R^d and R^e together with the atoms to which they are attached form a heterocyclic ring of 5 to 7 members containing 0-2 additional heteroatoms independently selected from oxygen, sulfur and nitrogen;

- R^f and R^g are independently selected from hydrogen, C_{1-10} alkyl, Cy and Cy- C_{1-10} alkyl wherein Cy is optionally substituted with C_{1-10} alkyl; or
- 15 R^f and R^g together with the carbon to which they are attached form a ring of 5 to 7 members containing 0-2 heteroatoms independently selected from oxygen, sulfur and nitrogen;

- R^h is
- 20 1) hydrogen,
 - 2) C_{1-10} alkyl,
 - 3) C_{2-10} alkenyl,
 - 4) C_{2-10} alkynyl,
 - 5) cyano,
 - 6) aryl,
 - 25 7) aryl C_{1-10} alkyl,
 - 8) heteroaryl,
 - 9) heteroaryl C_{1-10} alkyl, or
 - 10) $-\text{SO}_2\text{R}^i$;

- wherein alkyl, alkenyl, and alkynyl are optionally substituted with one to
- 30 four substituents independently selected from R^a ; and aryl and heteroaryl are each optionally substituted with one to four substituents independently selected from R^b ;

- R^i
- 1) C₁₋₁₀alkyl,
 - 2) C₂₋₁₀alkenyl,
 - 3) C₂₋₁₀alkynyl, or
 - 4) aryl;

5 wherein alkyl, alkenyl, alkynyl and aryl are each optionally substituted with one to four substituents independently selected from R^c ;

- R^x is
- 1) $-OR^d$,
 - 2) $-NO_2$,
 - 10 3) halogen
 - 4) $-S(O)_mR^d$,
 - 5) $-SR^d$,
 - 6) $-S(O)_2OR^d$,
 - 7) $-S(O)_mNR^dRe$,
 - 15 8) $-NR^dRe$,
 - 9) $-O(CR^fRg)_nNR^dRe$,
 - 10) $-C(O)R^d$,
 - 11) $-CO_2R^d$,
 - 12) $-CO_2(CR^fRg)_nCONR^dRe$,
 - 20 13) $-OC(O)R^d$,
 - 14) $-CN$,
 - 15) $-C(O)NR^dRe$,
 - 16) $-NR^dC(O)Re$,
 - 17) $-OC(O)NR^dRe$,
 - 25 18) $-NR^dC(O)ORE$,
 - 19) $-NR^dC(O)NR^dRe$,
 - 20) $-CR^d(N-ORE)$,
 - 21) $-CF_3$,
 - 22) oxo,
 - 30 23) $NR^dC(O)NR^dSO_2R^i$,
 - 24) $NR^dS(O)_mRe$,
 - 25) $-OS(O)_2OR^d$, or
 - 26) $-OP(O)(OR^d)_2$;

- RY is
- 1) a group selected from R^x,
 - 2) C₁₋₁₀ alkyl,
 - 3) C₂₋₁₀ alkenyl,
 - 5 4) C₂₋₁₀ alkynyl,
 - 5) aryl C₁₋₁₀alkyl,
 - 6) heteroaryl C₁₋₁₀ alkyl,
 - 7) cycloalkyl,
 - 8) heterocyclyl;
- 10 wherein alkyl, alkenyl, alkynyl and aryl are each optionally substituted with one to four substituents independently selected from R^x;

Cy is cycloalkyl, heterocyclyl, aryl, or heteroaryl;

- 15 m is an integer from 1 to 2;

n is an integer from 1 to 10;

- X is
- 1) -C(O)OR^d,
 - 20 2) -P(O)(OR^d)(OR^e)
 - 3) -P(O)(R^d)(OR^e)
 - 4) -S(O)_mOR^d,
 - 5) -C(O)NR^dR^h, or
 - 6) -5-tetrazolyl;

25

- Y is
- 1) -C(O)-,
 - 2) -O-C(O)-,
 - 3) -NR^e-C(O)-,
 - 4) -S(O)₂-,
 - 30 5) -P(O)(OR⁴) or
 - 6) C(O)C(O);

Z and A are independently selected from -C- and -C-C-;

B is selected from the group consisting of

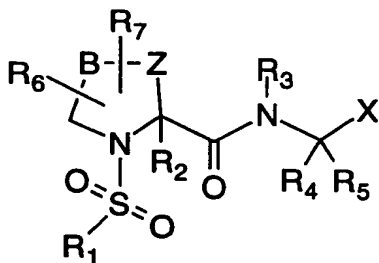
- 1) a bond,
- 2) -C-
- 5 3) -C-C-,
- 3) -C=C-,
- 4) a heteroatom selected from the group consisting of nitrogen, oxygen, and sulfur; and
- 5) -S(O)_m-.

10 In one embodiment of the method compounds of Formula I are those wherein Y is S(O)₂ and R¹ is C₁₋₁₀alkyl, Cy or Cy-C₁₋₁₀ alkyl wherein alkyl is optionally substituted with one to two substituents independently selected from R^a, and Cy is optionally substituted with one to four substituents independently selected from R^b.

15 In another embodiment of the method compounds of Formula I are those of formula Ia, Ib or Ic.

In another embodiment, the cell adhesion is mediated by VLA-4.

20 Another aspect of the present invention provides novel compounds of Formula Ia:



Ia

25

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined under formula I with the proviso that R₆/R₇ is not oxo when attached to the carbon between N and B, and with the further proviso

that when B and Z are each C, R², R³, R⁶, and R⁷ are each H, then R¹ is other than phenyl, 4-methylphenyl and 5-(NR^dRe)naphthyl.

In one subset of Formula Ia are compounds wherein Z is C.

In another subset of Formula Ia are compounds wherein B
5 is C, C=C, C-C or S. Preferably B is C or C=C.

In another subset of Formula Ia are compounds wherein X
is C(O)OR^d.

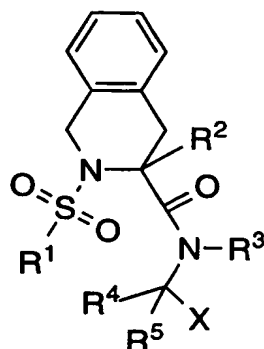
In another subset of Formula Ia are compounds wherein
R¹ is C₁₋₁₀alkyl, Cy or Cy-C₁₋₁₀alkyl wherein alkyl is optionally
10 substituted with one to two substituents independently selected from R^a,
and Cy is optionally substituted with one to four substituents
independently selected from R^b. For the purpose of R¹ Cy is preferably
aryl optionally substituted with one to four substituents selected from R^b.
More preferred R¹ is phenyl with a substituent on the 3-position and
15 optionally a second substituent; the more preferred substituents are
selected from C₁₋₁₀alkoxy, halogen, cyano, and trifluoromethyl.

In another subset of Formula Ia are compounds wherein
R² is H or C₁₋₆alkyl. Preferred R² is H or C₁₋₃alkyl, more preferably H
or methyl.

20 In another subset of Formula Ia are compounds wherein
R³ is H or C₁₋₆alkyl. Preferred R³ is H or C₁₋₃alkyl, more preferably H
or methyl.

In another subset of Formula Ia are compounds wherein
R⁵ is H and R⁴ is C₁₋₁₀alkyl or Cy-C₁₋₁₀alkyl, wherein alkyl is optionally
25 substituted with one to four substituents selected from phenyl and R_x,
and Cy is optionally substituted with one to four substituents
independently selected from R_y; or R⁴, R⁵ and the carbon to which they
are attached together form a 3-7 membered mono- or bicyclic carbon only
ring. For the purpose of R⁴, Cy is preferably aryl, more preferably
30 phenyl. In a preferred embodiment, R⁴ is phenyl-C₁₋₃alkyl, wherein
phenyl is optionally substituted with one or two groups selected from R_y.

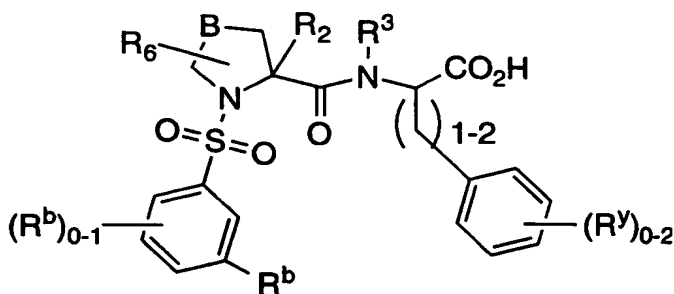
In one embodiment of compounds of formula Ia are
compounds of formula Ib:



Ib

- 5 wherein R² is H or C₁₋₆ alkyl, and R¹, R³, R⁴ and R⁵ are as defined previously under Formula I. In a preferred embodiment X is CO₂H; R¹ is aryl optionally substituted with one to four substituents selected from R^b; R² is H; R³ is H or C₁₋₃ alkyl; R⁴ is phenyl-C₁₋₃alkyl, wherein phenyl is optionally substituted with one or two groups selected from R^y;
 10 and R⁵ is H.

Another embodiment of compounds of Formula Ia are compounds of the formula Ic:

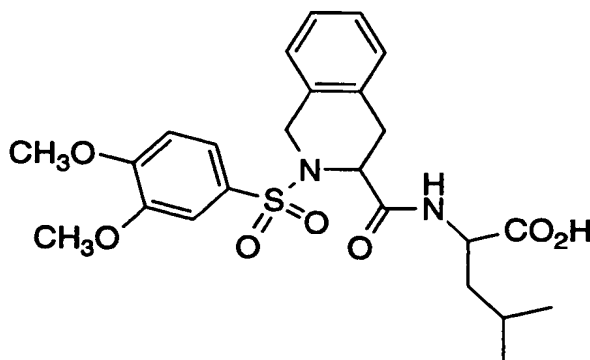


Ic

- 15 wherein R² is H or C₁₋₃ alkyl, R⁶ is H, C₁₋₆ alkyl, aryl, OR^d, SR^d, NR^dRe, or NR^dC(O)Re, B is S, C=C, C or C-C, R³ is H or C₁₋₆alkyl, R^b and R^y are as defined under Formula I. Preferably B is C and R^b is halogen, C₁₋₁₀alkoxy, cyano, or trifluoromethyl.
 20

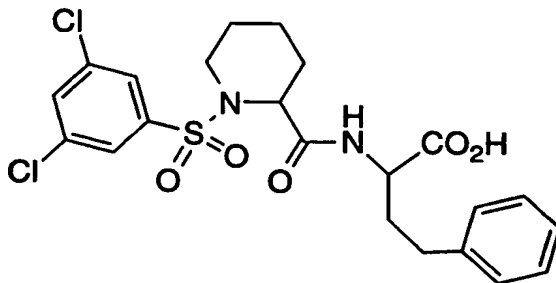
The present compounds are generally composed of three domains: 1) an acyl (including sulfonyl) moiety, 2) a cyclic amino acid 1, and 3) amino acid 2, and are named in a manner similar to that used to name oligopeptides. Representative names used herein and their
5 corresponding structures are shown below (without the stereochemistry) to illustrate the nomenclature used in the application.

N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-leucine



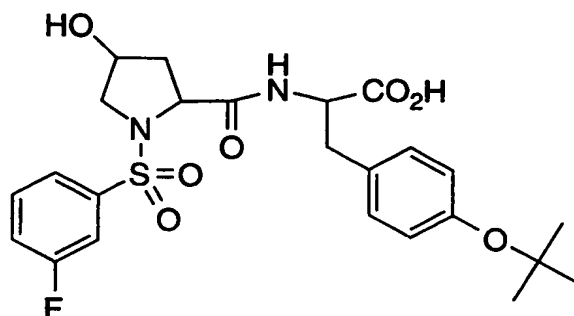
10

N-(3,5-dichlorobenzenesulfonyl)-(L)-pipecolyl-(L)-homophenylalanine

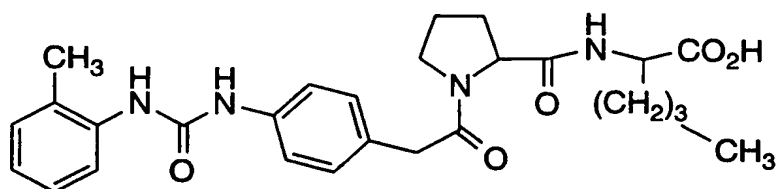


15

N-(3-fluorobenzenesulfonyl)-(L)-4(R)-hydroxypropyl-(L)-tyrosine, O-tert-butyl ether



N-[4-(N'-2-toluyllureido)phenylacetyl-(L)-prolyl-(L)-norleucine



5

"Alkyl", as well as other groups having the prefix "alk", such as alkoxy, alkanoyl, means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl, octyl, nonyl, and the like.

"Alkenyl" means carbon chains which contain at least one carbon-carbon double bond, and which may be linear or branched or combinations thereof. Examples of alkenyl include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, and the like.

"Alkynyl" means carbon chains which contain at least one carbon-carbon triple bond, and which may be linear or branched or combinations thereof. Examples of alkynyl include ethynyl, propargyl, 3-methyl-1-pentynyl, 2-heptynyl and the like.

"Cycloalkyl" means mono- or bicyclic saturated carbocyclic rings, each of which having from 3 to 10 carbon atoms. The term also includes monocyclic rings fused to an aryl group in which the point of attachment is on the non-aromatic portion. Examples of cycloalkyl

include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, tetrahydronaphthyl, decahydronaphthyl, indanyl, and the like.

"Aryl" means mono- or bicyclic aromatic rings containing only carbon atoms. The term also includes aryl group fused to a
5 monocyclic cycloalkyl or monocyclic heterocyclyl group in which the point of attachment is on the aromatic portion. Examples of aryl include phenyl, naphthyl, indanyl, indenyl, tetrahydronaphthyl, 2,3-dihydrobenzofuranyl, benzopyranyl, 1,4-benzodioxanyl, and the like.

"Heteroaryl" means a mono- or bicyclic aromatic ring
10 containing at least one heteroatom selected from N, O and S, with each ring containing 5 to 6 atoms. Examples of heteroaryl include pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridyl, oxazolyl, oxadiazolyl, thiadiazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, triazinyl, thienyl, pyrimidyl, pyridazinyl, pyrazinyl, benzoxazolyl, benzothiazolyl,
15 benzimidazolyl, benzofuranyl, benzothiophenyl, furo(2,3-b)pyridyl, quinolyl, indolyl, isoquinolyl, and the like.

"Heterocyclyl" means mono- or bicyclic saturated rings containing at least one heteroatom selected from N, S and O, each of said ring having from 3 to 10 atoms in which the point of attachment may be
20 carbon or nitrogen. The term also includes monocyclic heterocycle fused to an aryl or heteroaryl group in which the point of attachment is on the non-aromatic portion. Examples of "heterocyclyl" include pyrrolidinyl, piperidinyl, piperazinyl, imidazolidinyl, 2,3-dihydrofuro(2,3-b)pyridyl, benzoxazinyl, tetrahydrohydroquinolinyl, tetrahydroisoquinolinyl,
25 dihydroindolyl, and the like. The term also includes partially unsaturated monocyclic rings that are not aromatic, such as 2- or 4-pyridones attached through the nitrogen or N-substituted-(1H,3H)-pyrimidine-2,4-diones (N-substituted uracils).

"Halogen" includes fluorine, chlorine, bromine and iodine.
30

Optical Isomers - Diastereomers - Geometric Isomers - Tautomers

Compounds of Formula I contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single

enantiomers, diastereomeric mixtures and individual diastereomers. The present invention is meant to comprehend all such isomeric forms of the compounds of Formula I.

Some of the compounds described herein contain olefinic
5 double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

Some of the compounds described herein may exist with different points of attachment of hydrogen, referred to as tautomers. Such an example may be a ketone and its enol form known as keto-enol
10 tautomers. The individual tautomers as well as mixture thereof are encompassed with compounds of Formula I.

Compounds of the Formula I may be separated into diastereoisomeric pairs of enantiomers by, for example, fractional crystallization from a suitable solvent, for example methanol or ethyl
15 acetate or a mixture thereof. The pair of enantiomers thus obtained may be separated into individual stereoisomers by conventional means, for example by the use of an optically active acid as a resolving agent.

Alternatively, any enantiomer of a compound of the general Formula I or Ia may be obtained by stereospecific synthesis using
20 optically pure starting materials or reagents of known configuration.

Salts

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids
25 including inorganic or organic bases and inorganic or organic acids. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and
30 sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine,

betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine,
5 methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids,
10 including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-
15 toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

It will be understood that, as used herein, references to the compounds of Formula I are meant to also include the pharmaceutically
20 acceptable salts.

Utilities

The ability of the compounds of Formula I to antagonize the actions of VLA-4 and/or $\alpha 4\beta 7$ integrin makes them useful for preventing
25 or reversing the symptoms, disorders or diseases induced by the binding of VLA-4 and or $\alpha 4\beta 7$ to their various respective ligands. Thus, these antagonists will inhibit cell adhesion processes including cell activation, migration, proliferation and differentiation. Accordingly, another aspect of the present invention provides a method for the treatment
30 (including prevention, alleviation, amelioration or suppression) of diseases or disorders or symptoms mediated by VLA-4 and/or $\alpha 4\beta 7$ binding and cell adhesion and activation, which comprises administering to a mammal an effective amount of a compound of

Formula I. Such diseases, disorders, conditions or symptoms are for example (1) multiple sclerosis, (2) asthma, (3) allergic rhinitis, (4) allergic conjunctivitis, (5) inflammatory lung diseases, (6) rheumatoid arthritis, (7) septic arthritis, (8) type I diabetes, (9) organ transplantation rejection, (10) restenosis, (11) autologous bone marrow transplantation, (12) inflammatory sequelae of viral infections, (13) myocarditis, (14) inflammatory bowel disease including ulcerative colitis and Crohn's disease, (15) certain types of toxic and immune-based nephritis, (16) contact dermal hypersensitivity, (17) psoriasis, (18) tumor metastasis, and (19) atherosclerosis.

Dose Ranges

The magnitude of prophylactic or therapeutic dose of a compound of Formula I will, of course, vary with the nature of the severity of the condition to be treated and with the particular compound of Formula I and its route of administration. It will also vary according to the age, weight and response of the individual patient. In general, the daily dose range lie within the range of from about 0.001 mg to about 100 mg per kg body weight of a mammal, preferably 0.01 mg to about 50 mg per kg, and most preferably 0.1 to 10 mg per kg, in single or divided doses. On the other hand, it may be necessary to use dosages outside these limits in some cases.

For use where a composition for intravenous administration is employed, a suitable dosage range is from about 0.001 mg to about 25 mg (preferably from 0.01 mg to about 1 mg) of a compound of Formula I per kg of body weight per day and for cytoprotective use from about 0.1 mg to about 100 mg (preferably from about 1 mg to about 100 mg and more preferably from about 1 mg to about 10 mg) of a compound of Formula I per kg of body weight per day.

In the case where an oral composition is employed, a suitable dosage range is, e.g. from about 0.01 mg to about 100 mg of a compound of Formula I per kg of body weight per day, preferably from about 0.1 mg to about 10 mg per kg and for cytoprotective use from 0.1 mg

to about 100 mg (preferably from about 1 mg to about 100 mg and more preferably from about 10 mg to about 100 mg) of a compound of Formula I per kg of body weight per day.

- For the treatment of diseases of the eye, ophthalmic preparations for ocular administration comprising 0.001-1% by weight solutions or suspensions of the compounds of Formula I in an acceptable ophthalmic formulation may be used.

Pharmaceutical Compositions

- Another aspect of the present invention provides pharmaceutical compositions which comprises a compound of Formula I and a pharmaceutically acceptable carrier. The term "composition", as in pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) (pharmaceutically acceptable excipients) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of Formula I, additional active ingredient(s), and pharmaceutically acceptable excipients.

- Any suitable route of administration may be employed for providing a mammal, especially a human with an effective dosage of a compound of the present invention. For example, oral, rectal, topical, parenteral, ocular, pulmonary, nasal, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like.

- The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic

ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic bases or acids and organic bases or acids.

The compositions include compositions suitable for oral, 5 rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (aerosol inhalation), or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently 10 presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

For administration by inhalation, the compounds of the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or nebulisers. The 15 compounds may also be delivered as powders which may be formulated and the powder composition may be inhaled with the aid of an insufflation powder inhaler device. The preferred delivery systems for inhalation are metered dose inhalation (MDI) aerosol, which may be formulated as a suspension or solution of a compound of Formula I in 20 suitable propellants, such as fluorocarbons or hydrocarbons and dry powder inhalation (DPI) aerosol, which may be formulated as a dry powder of a compound of Formula I with or without additional excipients.

Suitable topical formulations of a compound of formula I 25 include transdermal devices, aerosols, creams, ointments, lotions, dusting powders, and the like.

In practical use, the compounds of Formula I can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical 30 compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical

media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, capsules and tablets, with the solid oral preparations being preferred over the liquid preparations. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

In addition to the common dosage forms set out above, the compounds of Formula I may also be administered by controlled release means and/or delivery devices such as those described in U.S. Patent Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; 3,630,200 and 4,008,719.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient, as a powder or granules or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet may be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent,

surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Desirably, each tablet contains from about 1 mg to about 500 mg of the active ingredient and each cachet or capsule contains from about 1 to about 500 mg of the active ingredient.

The following are examples of representative pharmaceutical dosage forms for the compounds of Formula I:

	<u>Injectable Suspension (I.M.)</u>	<u>mg/mL</u>
10	Compound of Formula I	10
	Methylcellulose	5.0
	Tween 80	0.5
	Benzyl alcohol	9.0
	Benzalkonium chloride	1.0
15	Water for injection to a total volume of 1 mL	
	<u>Tablet</u>	<u>mg/tablet</u>
	Compound of Formula I	25
	Microcrystalline Cellulose	415
20	Povidone	14.0
	Pregelatinized Starch	43.5
	Magnesium Stearate	<u>2.5</u>
		500
25	<u>Capsule</u>	<u>mg/capsule</u>
	Compound of Formula I	25
	Lactose Powder	573.5
	Magnesium Stearate	<u>1.5</u>
		600
30	<u>Aerosol</u>	<u>Per canister</u>
	Compound of Formula I	24 mg
	Lecithin, NF Liquid Concentrate	1.2 mg

Trichlorofluoromethane, NF	4.025 g
Dichlorodifluoromethane, NF	12.15 g

Combination Therapy

- 5 Compounds of Formula I may be used in combination with other drugs that are used in the treatment/prevention/suppression or amelioration of the diseases or conditions for which compounds of Formula I are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or
- 10 sequentially with a compound of Formula I. When a compound of Formula I is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of Formula I is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that
- 15 also contain one or more other active ingredients, in addition to a compound of Formula I. Examples of other active ingredients that may be combined with a compound of Formula I, either administered separately or in the same pharmaceutical compositions, include, but are not limited to:
- 20 (a) other VLA-4 antagonists such as those described in US 5,510,332, WO97/03094, WO97/02289, WO96/40781, WO96/22966, WO96/20216, WO96/01644, WO96/06108, WO95/15973 and WO96/31206; (b) steroids such as beclomethasone, methylprednisolone, betamethasone, prednisone, dexamethasone, and hydrocortisone; (c) immunosuppressants such as
- 25 cyclosporin, tacrolimus, rapamycin and other FK-506 type immunosuppressants; (d) antihistamines (H1-histamine antagonists) such as bromopheniramine, chlorpheniramine, dexchlorpheniramine, triprolidine, clemastine, diphenhydramine, diphenylpyraline, tripeleminamine, hydroxyzine, methdilazine, promethazine,
- 30 trimeprazine, azatadine, cypheptadine, antazoline, pheniramine pyrilamine, astemizole, terfenadine, loratadine, cetirizine, fexofenadine, descarboethoxyloratadine, and the like; (e) non-steroidal anti-asthmatics such as β 2-agonists (terbutaline, metaproterenol,

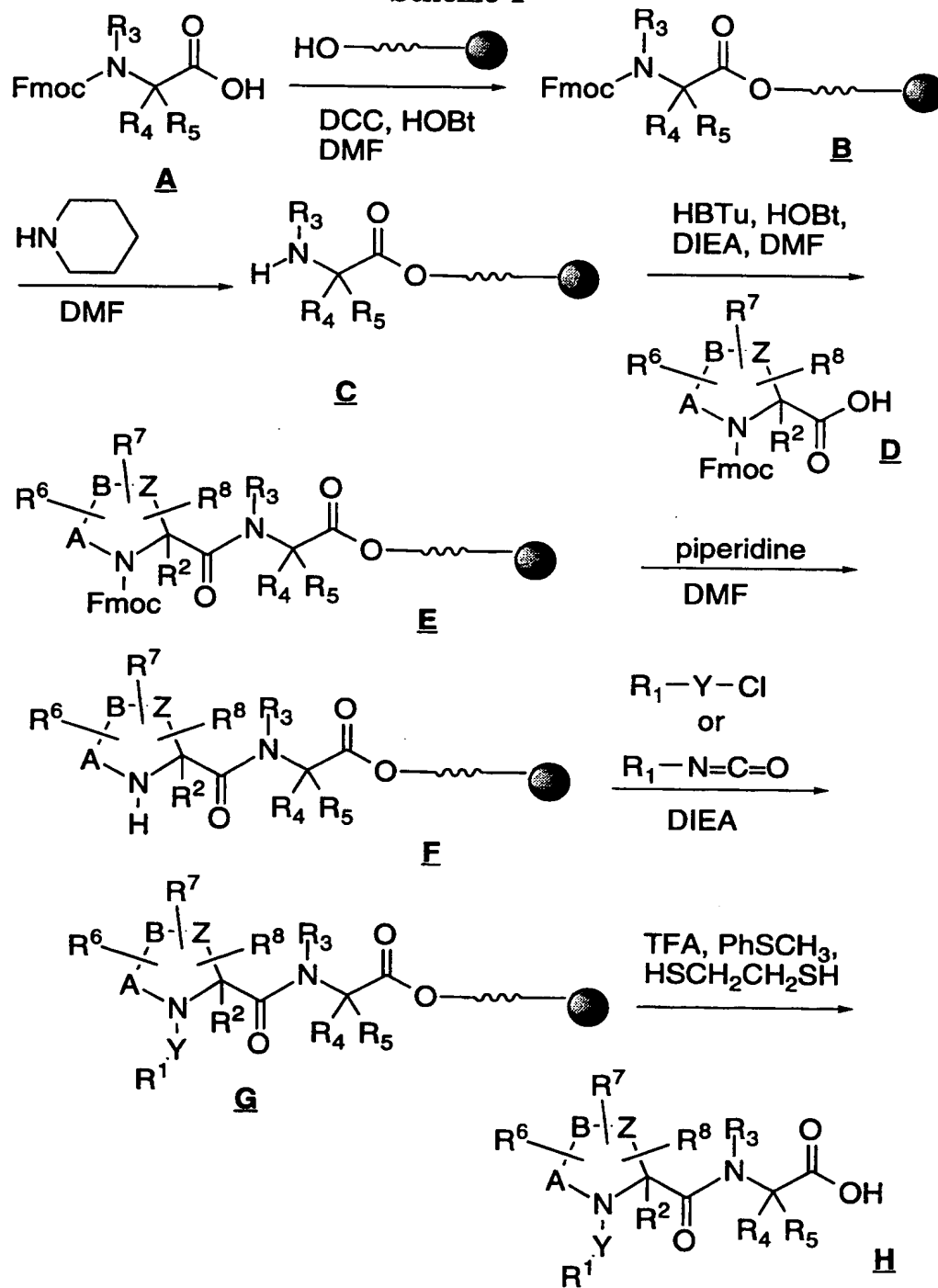
- fenoterol, isoetharine, albuterol, bitolterol, salmeterol and pirbuterol), theophylline, cromolyn sodium, atropine, ipratropium bromide, leukotriene antagonists (zafirlukast, montelukast, pranlukast, iralukast, pobilukast, SKB-106,203), leukotriene biosynthesis inhibitors
- 5 (zileuton, BAY-1005); (f) non-steroidal antiinflammatory agents (NSAIDs) such as propionic acid derivatives (alminoprofen, benoxaprofen, bucloxic acid, carprofen, fenbufen, fenoprofen, fluprofen, flurbiprofen, ibuprofen, indoprofen, ketoprofen, miroprofen, naproxen, oxaprozin, pirprofen, pranoprofen, suprofen, tiaprofenic acid, and
- 10 tioxaprofen), acetic acid derivatives (indomethacin, acemetacin, alclofenac, clidanac, diclofenac, fenclofenac, fenclozic acid, fentiazac, furofenac, ibufenac, isoxepac, oxpinac, sulindac, tiopinac, tolmetin, zidometacin, and zomepirac), fenamic acid derivatives (flufenamic acid, meclofenamic acid, mefenamic acid, niflumic acid and tolfenamic acid),
- 15 biphenylcarboxylic acid derivatives (diflunisal and flufenisal), oxicams (isoxicam, piroxicam, sudoxicam and tenoxicam), salicylates (acetyl salicylic acid, sulfasalazine) and the pyrazolones (apazone, bezpiperylon, feprazone, mofebutazone, oxyphenbutazone, phenylbutazone); (g) cyclooxygenase-2 (COX-2) inhibitors such as
- 20 celecoxib; (h) inhibitors of phosphodiesterase type IV (PDE-IV); (i) antagonists of the chemokine receptors, especially CCR-1, CCR-2, and CCR-3; (j) cholesterol lowering agents such as HMG-CoA reductase inhibitors (lovastatin, simvastatin and pravastatin, fluvastatin, atorvastatin, and other statins), sequestrants (cholestyramine and
- 25 colestipol), nicotinic acid, fenofibric acid derivatives (gemfibrozil, clofibrat, fenofibrate and benzaifibrate), and probucol; (k) anti-diabetic agents such as insulin, sulfonylureas, biguanides (metformin), α -glucosidase inhibitors (acarbose) and glitazones (troglitazone, pioglitazone, englitazone, MCC-555, BRL49653 and the like); (l)
- 30 preparations of interferon beta (interferon beta-1a, interferon beta-1b); (m) anticholinergic agents such as muscarinic antagonists (ipratropium bromide); (n) other compounds such as 5-aminosalicylic

acid and prodrugs thereof, antimetabolites such as azathioprine and 6-mercaptopurine, and cytotoxic cancer chemotherapeutic agents.

The weight ratio of the compound of the Formula I to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the Formula I is combined with an NSAID the weight ratio of the compound of the Formula I to the NSAID will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the Formula I and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

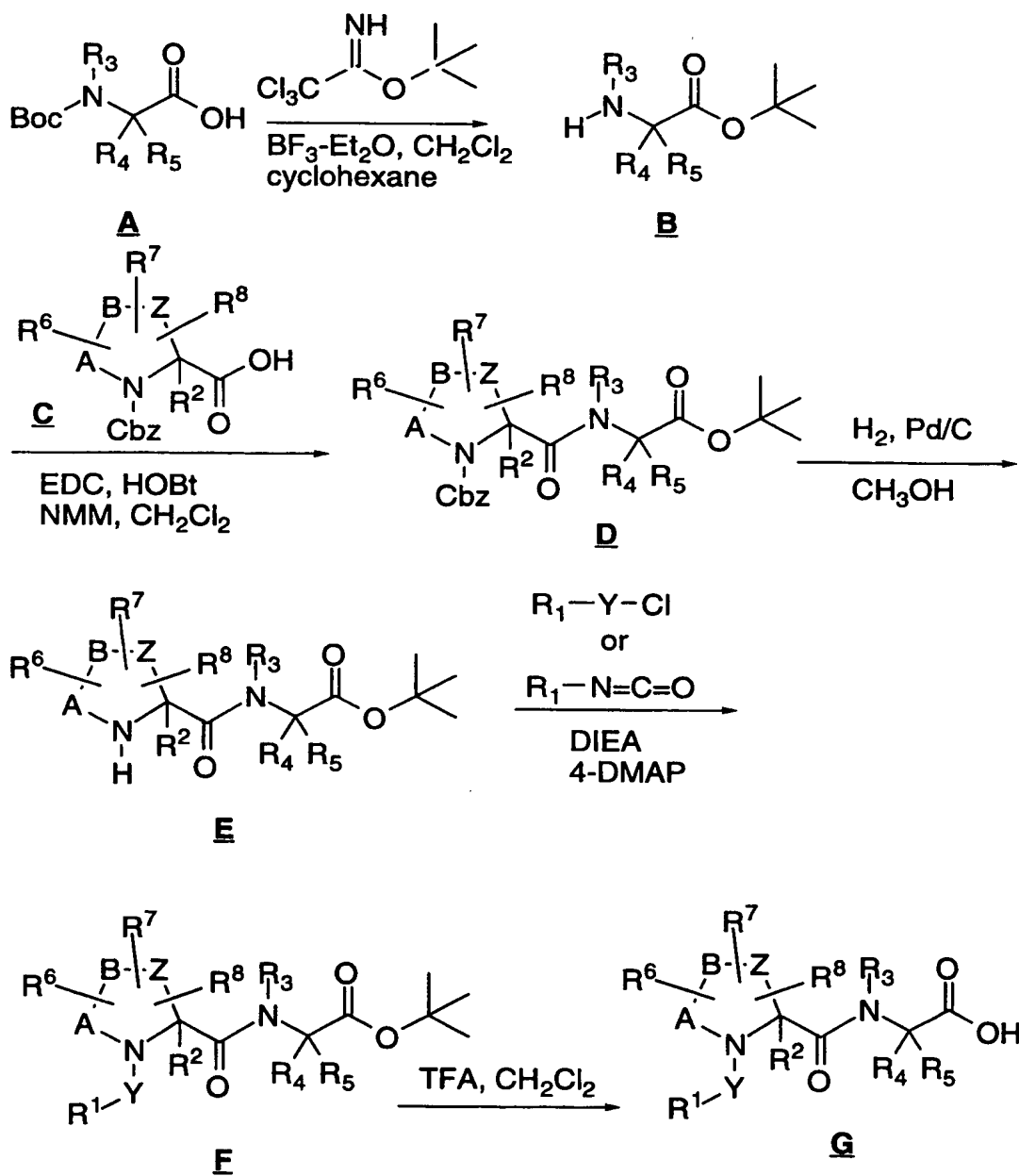
Compounds of the present invention may be prepared by procedures illustrated in the accompanying schemes. In the first method (Scheme 1), a resin-based synthetic strategy is outlined where the resin employed is represented by the ball (●). An N-Fmoc-protected amino acid derivative A (Fmoc = fluorenylmethoxycarbonyl) is loaded on to the appropriate hydroxyl-containing resin using dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBt) in dimethylformamide (DMF) to give B. The Fmoc protecting group is removed with piperidine in DMF to yield free amine C. The next Fmoc-protected amino acid derivative D is coupled to C employing standard peptide (in this instance, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), HOBt, and N,N-diisopropylethylamine (DIEA) in DMF) to yield dipeptide E. The Fmoc group is removed with piperidine in DMF to yield the free amine F. An acid chloride or isocyanate derivative is reacted with F in the presence of DIEA to yield G. The final product is removed from the resin with strong acid (in this instance, trifluoroacetic acid (TFA) in the presence of thioanisole and dithiane) to yield compounds of the present invention H.

Scheme 1



In the second method (Scheme 2), standard solution phase synthetic methodology is outlined. An N-Boc-protected amino acid derivative A (Boc = tert-butyloxycarbonyl) is treated with tert-butyl 2,2,2-trichloroacetimidate in the presence of boron trifluoride etherate to yield tert-butyl ester followed by treatment with strong acid (HCl in ethyl acetate or sulfuric acid in t-butyl acetate) to yield the free amine B which is subsequently coupled to Cbz-protected amino acid derivative C (Cbz = carbobenzyloxy) in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), HOBT, and N-methylmorpholine (NMM) in methylene chloride (Methylene chloride) to yield dipeptide D. Catalytic hydrogenation of D in the presence of a palladium-on-carbon (Pd/C) catalyst yields E. Reaction of E with an acylchloride or isocyanate in the presence of DIEA and 4-dimethylaminopyridine (DMAP) yields F which is subsequently reacted with strong acid (TFA) to yield the desired product G.

Scheme 2



GENERAL PROCEDURE FOR THE SOLID-PHASE SYNTHESIS OF COMPOUNDS OF FORMULA 1.

Step A. Loading of N-Fmoc-amino acid derivatives onto resins.

5 N-Fmoc-amino acids were loaded on either Wang® (Calbiochem-Novabiochem Corp.) or Chloro (2-chlorotriyl) resin. Wang® resin, typically 0.3 mmol, was washed with dimethylformamide three times. A solution of N-Fmoc-amino acid (0.3 mmol) in dimethylformamide (3 mL) was transferred to the pre-swollen Wang® resin. Dicyclohexylcarbodiimide (0.3 mmol) and 1-N-hydroxybenztriazole (0.3 mmol) was added and the mixture gently swirled for 2 hours. Following filtration, the resin was sequentially washed with dimethylformamide (3 times) and dichloromethane (3 times). The amino acid substitution value obtained after vacuum drying typically ranged between 0.07 to 0.1 mmol.

15 Alternatively, Chloro (2-chlorotriyl) resin, typically 0.2 mmol, was pre-swollen in dimethylformamide. A solution of N-Fmoc-amino acid (0.2 mmol) in dimethylformamide (3 ml) was added to the resin, followed by the addition of N,N-diisopropylethylamine (0.4 mmol). The resin was gently stirred for 2 hours, filtered and washed sequentially with dimethylformamide (3 times) and dichloromethane (3 times). The resin was finally washed with 10% methanol in dichloromethane and vacuum dried. The amino acid substitution value obtained after vacuum drying typically ranged between 0.05 to 0.1 mmol.

Step B. Deprotection of the N-Fmoc group.

30 The N-Fmoc protecting group was removed from the resin from Step A by treatment with 20% piperidine in dimethylformamide for 30 minutes. Following filtration, the resin was washed sequentially with dimethylformamide (3 times), dichloromethane (1 time) and dimethylformamide (2 times) and used in the subsequent reaction.

Step C. Coupling of the next N-Fmoc-amino acid derivative

A solution of the next desired N-Fmoc-amino acid derivative (0.4 mmol) in dimethylformamide (2 mL) was mixed with
5 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (0.4 mmol), 1-hydroxybenzotriazole (0.4 mmol) and diisopropylethylamine (0.6 mmol). This solution was transferred to resin from Step B and typically allowed to react for 2 hours. Couplings were monitored by ninhydrin reaction. The coupling
10 mixture was filtered and the resin washed with dimethylformamide (3 times) and used in the subsequent reaction.

Step D. Deprotection of the N-Fmoc group.

The N-Fmoc protecting group was removed from the
15 resin from Step C by the procedure described in Step B and used in the subsequent reaction.

Step E. Acylation (or sulfonylation) of the terminal amino group.

The desired N-terminal capping reagent (sulfonyl)
20 chloride or acyl chloride, or isocyanate) (0.4 mol) was dissolved in dimethylformamide (2 ml), mixed with N,N-diisopropylethylamine (0.8 mmol) and added to the resin from Step D. After approximately two hours, the resin was sequentially washed with dimethylformamide (3 times) and dichloromethane (3 times).
25

Step F. Cleavage of the desired products from the resins.

The final desired products were cleaved from the resins from Step E by gently stirring with a solution of trifluoroacetic acid:thioanisole:ethanedithiol (95:2.5:2.5); 3 hours for Wang® resin
30 and 30 minutes for the Chloro (2-chlorotriptyl) resin. Following filtration, the solvents were removed by evaporation and the residue dissolved in acetonitrile (3 mL). Insoluble material was removed by filtration. The final products were purified by reverse phase

chromatography with a linear gradient of buffer A (0.1% trifluoroacetic acid in water) and buffer B (0.1% trifluoroacetic acid in acetonitrile) and isolated by lyophilization. Molecular ions were obtained by electrospray ionization mass spectrometry or matrix-assisted laser desorption ionization time-of-flight mass spectrometry to confirm the structure of each peptide.

The following compounds were prepared by the general procedures described above using the appropriate amino acid derivatives and acyl or sulfonyl chloride or alkyl or aryl isocyanate. These examples are provided to illustrate the present invention and are not to be construed as limiting its scope in any manner.

Ex.	Compound Name	MS *
(1)	N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-leucine	491
(2)	N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-arginine	534
(3)	N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-glutamic acid	507
(4)	N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-glycine	435
(5)	N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-(1-naphthyl)alanine	575
(6)	N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)- α -t-butylglycine	491

(7)	N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-3-(2-thienyl)alanine	531
(8)	N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-cyclohexylalanine	531
(9)	N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-3-(2-naphthyl)alanine	575
(10)	N-(3,3-diphenylpropanoyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine	498
(11)	N-(2,4-dinitrobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine	521
(12)	N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-3,3-diphenylalanine	601
(13)	N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid	537
(14)	N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-proline	475
(15)	N-dansyl-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine	511
(16)	N-(2-naphthalenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine	481
(17)	N-(4-methoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine	461
(18)	N-(4-phenylbenzoyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine	471
(19)	N-(3,4-dimethylbenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-cysteine	481

(20)	N-(4-t-butylbenzenesulfonyl)-1,2,3,4-tetrahydro isoquinoline-3(S)-carbonyl-(L)-norleucine	487
(21)	N-(2,5-dichlorobenzenesulfonyl)-1,2,3,4- tetrahydro isoquinoline-3(S)-carbonyl-(L)- norleucine	498
(22)	N-(2-mesitylenesulfonyl)-1,2,3,4-tetrahydro isoquinoline-3(S)-carbonyl-(L)-norleucine	473
(23)	N-(p-toluenesulfonyl)-1,2,3,4-tetrahydro isoquinoline-3(S)-carbonyl-(L)-norleucine	444
(24)	N-(4-chlorobenzenesulfonyl)-1,2,3,4-tetrahydro isoquinoline-3(S)-carbonyl-(L)-norleucine	465
(25)	N-(N'-acetylsulfanilyl)-1,2,3,4-tetrahydro isoquinoline-3(S)-carbonyl-(L)-norleucine	488
(26)	N-(4-fluorobenzenesulfonyl)-1,2,3,4-tetrahydro isoquinoline-3(S)-carbonyl-(L)-norleucine	449
(27)	N-(1-naphthalenesulfonyl)-1,2,3,4-tetrahydro isoquinoline-3(S)-carbonyl-(L)-norleucine	481
(28)	N-(benzylsulfonyl)-1,2,3,4- tetrahydroisoquinoline-3(S)-carbonyl-(L)- norleucine	445
(29)	N-(4-nitrobenzenesulfonyl)-1,2,3,4-tetrahydro isoquinoline-3(S)-carbonyl-(L)-norleucine	476
(30)	N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4- tetrahydroisoquinoline-3(S)-carbonyl-(L)- phenylalanine	525
(31)	N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4- tetrahydroisoquinoline-3(S)-carbonyl-(L)- glutamine	506
(32)	N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4- tetrahydroisoquinoline-3(S)-carbonyl-(L)-(4- nitrophenyl)alanine	570

(33)	N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-asparagine	492
(34)	N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-methionine	509
(35)	N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-homophenylalanine	539
(36)	N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(D)-norleucine	491
(37)	N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-(4-fluorophenyl)alanine	543
(38)	N-(3-toluenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine	445
(39)	N-(4-trifluoromethylbenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine	499
(40)	N-(4-n-propylbenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine	473
(41)	N-(4-isopropylbenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine	473
(42)	N-(2,6-dichlorobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine	499
(43)	N-(4-ethylbenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine	459
(44)	N-(2,4-difluorobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine	467

(45)	N-(2-cyanobenzenesulfonyl)-1,2,3,4-tetrahydro isoquinoline-3(S)-carbonyl-(L)-norleucine	456
(46)	N-(4-tert-amylbenzenesulfonyl)-1,2,3,4- tetrahydro isoquinoline-3(S)-carbonyl-(L)- norleucine	501
(47)	N-(4-chloro-3-nitrobenzenesulfonyl)-1,2,3,4- tetrahydroisoquinoline-3(S)-carbonyl-(L)- norleucine	510
(48)	N-(3-cyanobenzoyl)-1,2,3,4-tetrahydro isoquinoline-3(S)-carbonyl-(L)-norleucine	420
(49)	N-(3,5-dichlorobenzenesulfonyl)-1,2,3,4- tetrahydroisoquinoline-3(S)-carbonyl-(L)- norleucine	499
(50)	N-(3,4-dichlorobenzenesulfonyl)-1,2,3,4- tetrahydroisoquinoline-3(S)-carbonyl-(L)- norleucine	499
(51)	N-(2-trifluoromethylbenzenesulfonyl)-1,2,3,4- tetrahydroisoquinoline-3(S)-carbonyl-(L)- norleucine	499
(52)	N-(2,3-dichlorobenzenesulfonyl)-1,2,3,4- tetrahydro isoquinoline-3(S)-carbonyl-(L)- norleucine	499
(53)	N-(2,4-dichlorobenzenesulfonyl)-1,2,3,4- tetrahydro isoquinoline-3(S)-carbonyl-(L)- norleucine	499
(54)	N-(2,5-dimethoxybenzenesulfonyl)-1,2,3,4- tetrahydroisoquinoline-3(S)-carbonyl-(L)- norleucine	491
(55)	N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4- tetrahydroisoquinoline-3(S)-carbonyl-(L)-serine	465
(56)	N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4- tetrahydroisoquinoline-3(S)-carbonyl-(L)- isoleucine	491

(57)	N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-tryptophan	564
(58)	N-(2,1,3-benzothiadiazole-4-sulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-tryptophan	489
(59)	N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-3-(3-pyridyl)alanine	526
(60)	N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-3-(2-naphthyl)alanine, ethyl ester	603
(61)	N-acetyl-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine	333
(62)	N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(R)-carbonyl-(D)-norleucine	491
(63)	N-propionyl-(L)-prolyl-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine	348
(64)	N-(4-cyanobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine	456
(65)	N-(benzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine	431
(66)	N-(3-nitrobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine	476
(67)	N-(3-trifluoromethylbenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine	499
(68)	N-(2-thienylsulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine	437
(69)	N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-N-methyllleucine	505

(70)	N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-citrulline	535
(71)	N-(4-iodobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine	557
(72)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-(3-iodo)tyrosine	613
(73)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-3-(3-pyridyl)alanine	472
(74)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-phenylalanine	471
(75)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-glutamic acid	453
(76)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-arginine	480
(77)	N-(N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl)-1-amino-cyclopentane-1-carboxylic acid	549
(78)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-3-(3,4-dichlorophenyl)alanine	541
(79)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-3-(2-naphthyl)alanine, ethyl ester	549
(80)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-3-(4-bromophenyl)alanine	550
(81)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-3-(4-nitrophenyl)alanine	516
(82)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-3-(4-thiazolyl)alanine	478
(83)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-3-(2-chlorophenyl)alanine	507
(84)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-3-(4-chlorophenyl)alanine	507
(85)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-3-(4-cyanophenyl)alanine	496

(86)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-tyrosine, O-sulfate	586
(87)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-3,5-diiodotyrosine	739
(88)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-tyrosine	488
(89)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-aspartic acid	438
(90)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-tryptophan	510
(91)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-methionine	454
(92)	N-(3,4-dimethoxybenzenesulfonyl)-(L)-prolyl-(L)-norleucine	429
(93)	N-(3,5-di(trifluoromethyl)benzenesulfonyl)-(L)-prolyl-(L)-3-(2-naphthyl)alanine	589
(94)	N-(3,4-dimethoxybenzenesulfonyl)-(L)-thiaprolyl-(L)-3-(2-naphthyl)alanine	531
(95)	N-(3,4-dimethoxybenzenesulfonyl)-(L)-thiaprolyl-(L)-norleucine	447
(96)	N-[4-(N'-2-toluy lureido)phenylacetyl]-(L)-thiaprolyl-(L)-3-(2-naphthyl)alanine	597
(97)	N-(3,5-dichlorobenzenesulfonyl)-(L)-thiaprolyl-(L)-3-(2-naphthyl)alanine	539
(98)	N-(3,4-dimethoxybenzenesulfonyl)-(L)-pipecolyl-(L)-norleucine	443
(99)	N-(3,4-dimethoxybenzenesulfonyl)-(L)-pipecolyl-(L)-norleucine, ethyl ester	471
(100)	N-(3,5-dichlorobenzenesulfonyl)-(L)-pipecolyl-(L)-homophenylalanine	499
(101)	N-(3,5-dichlorobenzenesulfonyl)-(L)-pipecolyl-(L)-(3-iodo)tyrosine	626

(102)	N-(3,5-dichlorobenzenesulfonyl)-(L)-pipecolyl-(L)-3-(2-naphthyl)alanine	535
(103)	N-[4-(N'-2-toluy lureido)phenylacetyl]-(L)-pipecoliny(L)-3-(2-naphthyl)alanine	593
(104)	N-[3,5-di(trifluoromethyl)benzenesulfonyl]-(L)-pipecolyl-(L)-3-(2-naphthyl)alanine	603
(105)	N-(3,4-dimethoxybenzenesulfonyl)-(L)-pipecolyl-(L)-3-(2-naphthyl)alanine, ethyl ester	555
(106)	N-(3,4-dimethoxybenzenesulfonyl)-(L)-octahydroisoquinoline-3-carbonyl-(L)-norleucine	483
(107)	N-(3,4-dimethoxybenzenesulfonyl)-azetidine-2-carbonyl-(L)-norleucine	415
(108)	N-(3,5-dichlorobenzenesulfonyl)-(L)-4(S)-hydroxypropyl-(L)-3-(2-naphthyl)alanine	537
(109)	N-(3,4-dimethoxybenzenesulfonyl)-(L)-4(S)-hydroxypropyl-(L)-norleucine	445
(110)	N-(3,4-dimethoxybenzenesulfonyl)-(L)-3,4-dehydropropyl-(L)-norleucine	427
(111)	N-(3-bis(N,N-benzenesulfonyl)aminobenzenesulfonyl)-(L)-propyl-(L)-norleucine	
(112)	N-(3,5-dichlorobenzenesulfonyl)-(L)-propyl-(L)-3-(4-pyridyl)alanine	472.2
(113)	N-(3,5-dichlorobenzenesulfonyl)-(L)-4(R)-aminopropyl-(L)-3-(2-naphthyl)alanine	536.1
(114)	N-(3,5-dichlorobenzenesulfonyl)-(L)-3,4-dehydropropyl-(L)-4-fluorophenylalanine	487.2
(115)	N-(3-chlorobenzenesulfonyl)-(L)-propyl-(L)-4-fluorophenylalanine	455.1
(116)	N-(3,5-dichlorobenzenesulfonyl)-(L)-4(R)-hydroxypropyl-(L)-4-fluorophenylalanine	505.2
(117)	N-(3,5-dichlorobenzenesulfonyl)-(L)-thiaprolyl-(L)-tyrosine	505.0

(118)	N-(3,5-dichlorobenzenesulfonyl)-(L)-thiaprolyl-(L)-3-iodotyrosine	631.0
(119)	N-(3-fluorobenzenesulfonyl)-(L)-thiaprolyl-(L)-3-(2-naphthyl)alanine	489.3
(120)	N-(3-fluorobenzenesulfonyl)-(L)-pipecolyl-(L)-3-(2-naphthyl)alanine	485.4
(121)	N-(3-fluorobenzenesulfonyl)-(L)-thiaprolyl-(L)-4-fluorophenylalanine	457.2
(122)	N-(3-fluorobenzenesulfonyl)-(L)-prolyl-(L)-4-fluorophenylalanine	439.2
(123)	N-(3-chlorobenzenesulfonyl)-(L)-3,4-dehydroprolyl-(L)-4-fluorophenylalanine	453.3
(124)	N-(3-fluorobenzenesulfonyl)-(L)-4(R)-hydroxyprolyl-(L)-4-fluorophenylalanine	455.0
(125)	N-(3-chlorobenzenesulfonyl)-(L)-4(R)-hydroxyprolyl-(L)-4-fluorophenylalanine	471.0
(126)	N-(3,5-dichlorobenzenesulfonyl)-(L)-pipecolyl-(L)-4-fluorophenylalanine	503.1
(127)	N-(3-fluorobenzenesulfonyl)-(L)-3,4-dehydroprolyl-(L)-tyrosine	435.3
(128)	N-(4,5-dichloro-2-thiophenesulfonyl)-(L)-prolyl-(L)-tyrosine	493.2
(129)	N-(3-fluorobenzenesulfonyl)-(L)-4(R)-hydroxyprolyl-(L)-tyrosine	453.2
(130)	N-(3-chlorobenzenesulfonyl)-(L)-4(R)-hydroxyprolyl-(L)-tyrosine	469.2
(131)	N-(3-fluorobenzenesulfonyl)-(L)-pipecolyl-(L)-4-fluorophenylalanine	453.3
(132)	N-(3-fluorobenzenesulfonyl)-(L)-4(R)-hydroxyprolyl-(L)-tyrosine, O-tert-butyl ether	509.1
(133)	N-(3-chlorobenzenesulfonyl)-(L)-4(R)-hydroxyprolyl-(L)-tyrosine, O-tert-butyl ether	525.3

(134)	N-(4,5-dichloro-2-thiophenesulfonyl)-(L)-3,4-dehydroprolyl-(L)-tyrosine	491.1
(135)	N-(3,5-dichlorobenzenesulfonyl)-(L)-3(S)-methylprolyl-(L)-4-fluorophenylalanine	503.1
(136)	N-(4,5-dichloro-2-thiophenesulfonyl)-(L)-3,4-dehydroprolyl-(L)-tyrosine	485.1
(137)	N-(3-fluorobenzenesulfonyl)-(L)-3,4-dehydroprolyl-(L)-tyrosine, O-tert-butyl ether	491.1
(138)	N-(3-chlorobenzenesulfonyl)-(L)-3,4-dehydroprolyl-(L)-tyrosine, O-tert-butyl ether	507.3
(139)	N-(3-chlorobenzenesulfonyl)-(L)-2(S)-methylprolyl-(L)-4-fluorophenylalanine	469.1
(140)	N-(3-chlorobenzenesulfonyl)-(L)-2(S)-methylprolyl-(L)-tyrosine	467.3
(141)	N-(3-chlorobenzenesulfonyl)-(L)-2(S)-methylprolyl-(L)-tyrosine, O-tert-butyl ether	523.2
(142)	N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methylprolyl-(L)-tyrosine	501.0
(143)	N-(3-fluorobenzenesulfonyl)-(L)-prolyl-(L)-3-iodotyrosine	563.1
(144)	N-(3-chlorobenzenesulfonyl)-(L)-prolyl-(L)-3-iodotyrosine	579.0
(145)	N-(3-fluorobenzenesulfonyl)-(L)-prolyl-(L)-3-phenylalanine	421.1
(146)	N-(3-chlorobenzenesulfonyl)-(L)-prolyl-(L)-phenylalanine	437.3
(147)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-phenylalanine	471.2
(148)	N-(3-fluorobenzenesulfonyl)-(L)-4(R)-hydroxyprolyl-(L)-phenylalanine	437.3
(149)	N-(3-chlorobenzenesulfonyl)-(L)-4(R)-hydroxyprolyl-(L)-phenylalanine	453.2

(150)	N-(4,5-dichloro-2-thiophenesulfonyl)-(L)-3,4-dehydroprolyl-(L)-3-(4-pyridyl)alanine	476.1
(151)	N-(4,5-dichloro-2-thiophenesulfonyl)-(L)-thiaprolyl-(L)-3-(4-pyridyl)alanine	495.9
(152)	N-(4,5-dichloro-2-thiophenesulfonyl)-(L)-3,4-dehydroprolyl-(L)-4-fluorophenylalanine	492.9
(153)	N-(3,5-dichlorobenzenesulfonyl)-(L)-4(R)-hydroxyprolyl-(L)-phenylalanine	487.1
(154)	N-(3-trifluoromethylbenzenesulfonyl)-(L)-prolyl-(L)-4-fluorophenylalanine	489.3
(155)	N-(3-trifluoromethylbenzenesulfonyl)-(L)-thiaprolyl-(L)-4-fluorophenylalanine	507.0
(156)	N-(3-fluorobenzenesulfonyl)-(L)-3,4-dehydroprolyl-(L)-4-fluorophenylalanine	437.1
(157)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-tyrosine, O-phosphoric acid	567.0
(158)	N-(3-chlorobenzenesulfonyl)-(L)-4(R)-aminoprolyl-(L)-tyrosine	468.3
(159)	N-(4,5-dichloro-2-thiophenesulfonyl)-(L)-thiaprolyl-(L)-tyrosine	510.9
(160)	N-(N ₁ -methyl-4-imidazolesulfonyl)-(L)-prolyl-(L)-4-fluorophenylalanine	425.3
(161)	N-(3,5-dichlorobenzenesulfonyl)-(D)-prolyl-(D)-4-fluorophenylalanine	489.1
(162)	N-(4,5-dichloro-2-thiophenesulfonyl)-(L)-4(R)-aminoprolyl-(L)-3-(4-pyridyl)alanine	492.9
(163)	N-(5-(5-trifluoromethyl-2-pyridylsulfonyl)-2-thiophenesulfonyl)-(L)-prolyl-(L)-4-fluorophenylalanine	636.1
(164)	N-(5-(N-(4-chlorobenzoyl)aminomethyl))-2-thiophenesulfonyl)-(L)-prolyl-(L)-4-fluorophenylalanine	575.1

(165)	N-(5-(3-(1-methyl-5-trifluoromethyl-pyrazoyl))-2-thiophenesulfonyl)-(L)-prolyl-(L)-4-fluorophenylalanine	594.0
(166)	N-(3-fluorobenzenesulfonyl)-2(S)-methylprolyl-(L)-O-tert-butyl-tyrosine	507.3
(167)	N-(3-fluorobenzenesulfonyl)-(L)-4(R)-aminoprolyl-(L)-4-fluorophenylalanine	454.2
(168)	N-(3,5-dichlorobenzenesulfonyl)-(L)-4(R)-aminoprolyl-(L)-4-fluorophenylalanine	504.3
(169)	N-(3-chlorobenzenesulfonyl)-(L)-4(R)-aminoprolyl-(L)-4-fluorophenylalanine	470.1
(170)	N-(3,5-dichlorobenzenesulfonyl)-(L)-4(S)-aminoprolyl-(L)-4-fluorophenylalanine	504.0
(171)	N-(3-chlorobenzenesulfonyl)-(L)-thiaprolyl-(L)-4-fluorophenylalanine	473.3
(172)	N-(4-bromo-5-chloro-2-thiophenesulfonyl)-(L)-prolyl-(L)-4-fluorophenylalanine	540.9
(173)	N-(4,5-dichloro-2-thiophenesulfonyl)-(L)-prolyl-(L)-4-fluorophenylalanine	513.0
(174)	N-(3,5-dichlorobenzenesulfonyl)-(L)-thiaprolyl-(L)-3,5-diiodotyrosine	756.7
(175)	N-(5-benzoylamino-methyl-2-thiophenesulfonyl)-(L)-prolyl-(L)-4-fluorophenylalanine	560.1
(176)	N-(3-chlorobenzenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine	509.3
(177)	N-(5-benzenesulfonyl-2-thiophenesulfonyl)-(L)-prolyl-(L)-4-fluorophenylalanine	567.0
(178)	N-(3-bromo-5-chloro-2-thiophenesulfonyl)-(L)-prolyl-(L)-4-fluorophenylalanine	540.9
(179)	N-(3-chlorobenzenesulfonyl)-(L)-3,4-dehydroprolyl-(L)-tyrosine	451.2
(180)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-homophenylalanine	485.3

(181)	N-(4-benzenesulfonyl-2-thiophenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine	621.1
(182)	N-(5-benzoylaminomethyl-2-thiophenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine	614.2
(183)	N-(trans-2-phenyl-ethylene-sulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine	501.3
(184)	N-(5-benzenesulfonyl-2-thiophenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine	621.1
(185)	N-(3-fluorobenzenesulfonyl)-(L)-thiaprolyl-(L)-O-tert-butyl-tyrosine	511.2
(186)	N-(benzylsulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine	489.3
(187)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-cysteine, amide	426.2
(188)	N-(1-methyl-4-imidazolylsulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine	479.1
(189)	N-(4-(N-(4-dimethylaminophenyl)diazobenzenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine	622.0
(190)	N-(5-(4-trifluoromethylbenzenesulfonyl)-2-thiophenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine	690.2
(191)	N-(3-bromobenzenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine	553.2
(192)	N-(4-methylsulfonyl-benzenesulfonyl)-(L)-prolyl-(L)-4-fluorophenylalanine	499.2
(193)	N-(4-methoxybenzenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine	505.2
(194)	N-(4,5-dichloro-2-thiophenesulfonyl)-(L)-prolyl-(L)-3-fluorophenylalanine	495.0
(195)	N-(5-chloro-2-thiophenesulfonyl)-(L)-prolyl-(L)-4-fluorophenylalanine	461.1

(196)	N-(3-chlorobenzenesulfonyl)-(L)-thiaprolyl-(L)-tyrosine	471.0
(197)	N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methylprolyl-(L)-O-tert-butyl-tyrosine	558.6
(198)	N-(1(R)-(+)-10-camphorsulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine	549.3
(199)	N-(1(S)-(+)-10-camphorsulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine	549.3
(200)	N-(3,4-methylenedioxy-phenylacetyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine	497.2
(201)	N-(3-chlorobenzenesulfonyl)-(L)-4(R)-hydroxyprolyl-(L)-tyrosine-O-sulfate	551.0
(202)	N-(3-chlorobenzenesulfonyl)-(L)-thiaprolyl-(L)-tyrosine-O-sulfate	553.7
(203)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-cysteine	427.2
(204)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-N-methyl-isoleucine	451.2
(205)	N-(3,5-dichlorobenzenesulfonyl)-(L)-4(R)-aminoprolyl-(L)-O-tert-butyl-tyrosine	558.3
(206)	N-(3-chlorobenzenesulfonyl)-(L)-4(R)-aminoprolyl-(L)-O-tert-butyl-tyrosine	524.4
(207)	N-(3-cyanobenzenesulfonyl)-(L)-prolyl-(L)-tyrosine	444.3
(208)	N-benzenesulfonyl-(L)-prolyl-(L)-O-tert-butyl-tyrosine	475.5
(209)	N-(4-methylsulfonylbenzenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine	553.2
(210)	N-(4,5-dichloro-2-thiophenesulfonyl)-(L)-4(R)-aminoprolyl-(L)-O-tert-butyl-tyrosine	564.3
(211)	N-(4,5-dichloro-2-thiophenesulfonyl)-(L)-4(R)-aminoprolyl-(L)-4-fluorophenylalanine	510.1

(212)	N-(9-fluorenylmethyloxycarbonyl)-(L)-prolyl-(L)-phenylalanine	485
(213)	N-(benzenesulfonyl)-(L)-prolyl-(L)-phenylalanine	403
(214)	N-(n-octyl-1-sulfonyl)-(L)-prolyl-(L)-phenylalanine	418
(215)	N-(3-fluorobenzenesulfonyl)-(L)-5(R)-phenylprolyl-(L)-4-fluorophenylalanine	515
(216)	N-(3,5-dichlorobenzenesulfonyl)-(L)-3(R)-phenylprolyl-(L)-4-iodophenylalanine	582
(217)	N-(3,5-dichlorobenzenesulfonyl)-1,2,3,4-tetrahydro isoquinoline-1-carbonyl-(L)-4-fluorophenylalanine	568
(218)	N-(3,5-dichlorobenzenesulfonyl)-1,3-dihydro isoindolyl-1-carbonyl-(L)-4-fluorophenylalanine	554
(219)	N-(4-(fluorescien-4-carbonylamino)benzenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine	879.2
(220)	N-(3-ethoxycarbonyl-benzenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine	547.2
(221)	N-(4-iodobenzenesulfonyl)-(L)-prolyl-(L)-4-benzoyl-phenylalanine	633.0
(222)	N-(3-(4-benzophenonyl-carbonylamino)benzenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine	698.2
(223)	N-(3-(6-(biotinylamino)-n-hexanoyl)aminobenzenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine	829.4
(224)	N-(3,5-dichlorobenzenesulfonyl)-[3.1.0]-3-azabicyclohexane-2-carbonyl-(L)-4-fluorophenylalanine	518

* m/e: (M + 1 (H⁺))⁺ or (M + 18 (NH₄⁺))⁺

EXAMPLE 225

N-(3,5-Dichlorobenzenesulfonyl)-(L)-prolyl-(L)-3-(2-naphthyl)alanine.

Step A: (L)-3-(2-Naphthyl)alanine, tert-butyl ester, hydrochloride.

To a solution of N-Boc-2-naphthylalanine (1.0 g, 3.17 mmol) in a mixture of methylene chloride (7 mL) and cyclohexane (14 mL) were added t-butyl trichloroacetimidate (0.60 mL, 3.35 mmol) and boron trifluoride-etherate (60 μ L, 0.473 mmol). The reaction mixture was stirred for 5 hours at room temperature under a nitrogen atmosphere and then treated a second time with the same amounts of t-butyl trichloroacetimidate and boron trifluoride-etherate as above. After stirring overnight, the mixture was filtered and the filtrate evaporated. The product was obtained pure by silica gel chromatography eluting with 10% diethyl ether in hexane; yield 843 mg. The product was treated with 1M HCl in ethyl acetate (11.5 mL) for 18 hours at room temperature. The mixture was evaporated and coevaporated several times with diethyl ether to afford the title compound; yield 670 mg. 400 MHz ^1H NMR (CD_3OD): δ 1.38 (s, 9H); 3.29-3.46 (m, 2H); 4.28 (t, 1H); 7.40-7.90 (m, 7H).

Step B: N-(Benzyloxycarbonyl)-(L)-prolyl-(L)-3-(2-naphthyl)alanine, tert-butyl ester.

To a solution of N-(benzyloxycarbonyl)-(L)-proline (536 mg, 2.15 mmol) in methylene chloride (25 mL) were added 1-hydroxybenzotriazole (434 mg, 3.21 mmol), N-methylemorpholine (0.353 mL, 3.21 mmol), and (L)-2-naphthylalanine tert-butyl ester hydrochloride (660 mg, 2.14 mmol). After cooling in an ice-bath for 5 minutes, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (493 mg, 2.57 mmol) was added. After 15 minutes, the cooling bath was removed and the mixture stirred overnight under a nitrogen atmosphere. The mixture was diluted with methylene chloride, washed with water, 2N HCl, saturated NaHCO_3 solution, saturated brine solution, dried (anhydrous magnesium sulfate), and evaporated. Silica gel chromatography

eluting with 30% ethyl acetate in hexane afforded pure title compound; yield 877 mg (81%).

Step C: (L)-Prolyl-(L)-3-(2-naphthyl)alanine, tert-butyl ester.

- 5 A solution of N-(benzyloxycarbonyl)-(L)-prolyl-(L)-2-naphthylalanine tert-butyl ester (870 mg, 1.73 mmol) in methanol (30 mL) was hydrogenated under an atmosphere of hydrogen gas in the presence of 10% palladium-on-charcoal (75 mg) until complete disappearance of starting material (several hours) as indicated by
10 TLC (30% ethyl acetate in hexane). The catalyst was removed by filtration through Celite, the filter washed with methanol, and the combined filtrate and washings evaporated to afford an oil that crystallized upon standing; yield 604 mg (95%).
400 MHz ¹H NMR (CD₃OD): δ 1.40 (s, 9H); 2.00 (m, 1H); 2.79 (m, 2H);
15 3.16 (dd, 1H); 3.58 (dd, 1H); 4.67 (dd, 1H); 7.32-7.81 (m, 7H).

Step D: N-(3,5-Dichlorobenzenesulfonyl)-(L)-prolyl-(L)-3-(2-naphthyl)alanine, tert-butyl ester.

- To a solution of (L)-prolyl-(L)-2-naphthylalanine tert-butyl
20 ester (400 mg, 1.09 mmol) in methylene chloride (10 mL) were added N,N-diisopropylethylamine (470 μL, 2.70 mmol), 4-dimethylaminopyridine (13 mg, 0.106 mmol), and 3,5-dichlorobenzenesulfonyl chloride (320 mg, 1.30 mmol). The reaction mixture was stirred for 2 hours at room temperature, diluted with
25 methylene chloride, washed with water, 2N HCl, saturated NaHCO₃ solution, saturated brine solution, dried (Anhydrous magnesium sulfate), and evaporated. Pure title compound was obtained by silica gel chromatography eluting with 20% ethyl acetate in hexane; yield
501 mg (80%).
30 400 MHz ¹H NMR (CD₃OD): δ 1.40 (s, 9H); 1.53-1.89 (m, 4H); 3.20-3.45 (m, 4H); 4.20 (dd, 1H); 4.69 (dd, 1H); 7.40-7.80 (m, 10H).

Step E: N-(3,5-Dichlorobenzenesulfonyl)-(L)-prolyl-(L)-3-(2-naphthyl)alanine.

(224) A cooled solution of N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-2-naphthylalanine tert-butyl ester (497 mg, 0.861 mmol) in methylene chloride (25 mL) was treated with trifluoroacetic acid (3.5 mL, 0.045 mol). The cooling bath was removed, and the mixture was stirred until TLC (25% ethyl acetate in hexane) indicated complete disappearance of starting material. The reaction mixture was then evaporated, coevaporated with methylene chloride (3X), toluene (2X), and finally methanol. The product was dried under high vacuum; yield 445 mg (99%).
 MS: m/e 521 (M); 537 (M + NH₃)
 400 MHz ¹H NMR (CD₃OD): δ 1.51-1.87 (m, 4H); 3.19-3.46 (m, 4H); 4.20 (dd, 1H); 4.80 (dd, 1H); 7.39-7.82 (m, 10H).

The following compounds were prepared by the procedures described in Example 225 using the appropriate amino acid derivatives and acyl or sulfonyl chloride or alkyl or aryl isocyanate:

Ex.	Compound Name	MS *
(226)	N-[4-(N'-2-toluylyureido)phenylacetyl-(L)-prolyl-(L)-norleucine	495
(227)	N-(3,4-dimethoxybenzoyl)-(L)-prolyl-(L)-norleucine	393
(228)	N-(3,4-dimethoxybenzenesulfonyl)-(L)-pipecolyl-(L)-tryptophan	516
(229)	N-(4-nitrobenzenesulfonyl)-(L)-prolyl-(L)-norleucine	414
(230)	N-[3,5-di(trifluoromethyl)benzenesulfonyl]-(L)-prolyl-(L)-norleucine	505



(231)	N-(3,5-dichlorobenzenesulfonyl))-(L)-prolyl-(L)-norleucine	437
(232)	N-(3-trifluoromethylbenzenesulfonyl))-(L)-prolyl-(L)-norleucine	437
(233)	N-[4-(benzoylamino)benzenesulfonyl))-(L)-prolyl-(L)-norleucine	488
(234)	N-(4-methoxy-3,5-dinitrobenzenesulfonyl)-(L)-prolyl-(L)-norleucine	488
(235)	N-(3-chlorobenzenesulfonyl))-(L)-prolyl-(L)-norleucine	402
(236)	N-(3-trifluoromethylbenzenesulfonyl))-(L)-prolyl-(L)-3-(2-naphthyl)alanine	521
(237)	N-(3-nitrobenzenesulfonyl))-(L)-prolyl-(L)-norleucine	414
(238)	N-(3-cyanobenzenesulfonyl))-(L)-prolyl-(L)-norleucine	394
(239)	N-(3,5-dichlorobenzenesulfonyl))-(L)-prolyl-(L)-tryptophan	510
(240)	N-(3-methylbenzenesulfonyl))-(L)-prolyl-(L)-norleucine	383
(241)	N-(3,5-dichlorobenzenesulfonyl))-(L)-3(S)-methylprolyl-(L)-3-(2-naphthyl)alanine	535
(242)	N-(3-chlorobenzenesulfonyl)-(L)-prolyl-(L)-3-(2-naphthyl)alanine	488
(243)	N-(3-fluorobenzenesulfonyl))-(L)-prolyl-(L)-3-(2-naphthyl)alanine	471
(244)	N-phenylacetyl-(L)-prolyl-(L)-3-(2-naphthyl)alanine	431
(245)	N-(3-phenylpropionyl)-(L)-prolyl-(L)-3-(2-naphthyl)alanine	445
(246)	N-(phenylaminocarbonyl)-(L)-prolyl-(L)-3-(2-naphthyl)alanine	432

(247)	N-(3,5-dichlorobenzenesulfonyl)-(L)-2-methyl- prolyl-(L)-3-(2-naphthyl)-alanine	535
(248)	N-(benzenesulfonyl)-(L)-prolyl-(L)-3-(2- naphthyl)alanine	453
(249)	N-(4-N'-phenylureidobenzenesulfonyl)-(L)-prolyl- (L)-3-(2-naphthyl)alanine	587
(250)	N-(3-fluorobenzenesulfonyl)-(L)-5,5-dimethyl- prolyl-(L)-3-(2-naphthyl)alanine	499
(251)	N-(4-N'-(2-toluy)ureidobenzenesulfonyl)-(L)- prolyl-(L)-3-(2-naphthyl)alanine	601
(252)	N-(3-fluorobenzenesulfonyl)-(L)-prolyl-(L)-4- iodophenylalanine	547
(253)	N-(4-N'-benzylureidobenzenesulfonyl)-(L)-prolyl- (L)-3-(2-naphthyl)alanine	601
(254)	N-(phenyloxalyl)-(L)-prolyl-(L)-3-(2- naphthyl)alanine	445
(255)	N-(benzylaminocarbonyl)-(L)-prolyl-(L)-3-(2- naphthyl)alanine	445
(256)	N-(3-fluorobenzenesulfonyl)-(L)-2(S)-methyl- prolyl-(L)-4-fluorophenylalanine	470
(257)	N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl- prolyl-(L)-4-fluorophenylalanine	520
(258)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)- phenylalaninamide-N-methylsulfonamide	565
(259)	N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl- prolyl-(L)-4-iodophenylalanine	628
(260)	N-(3-fluorobenzenesulfonyl)-(L)-prolyl-(L)- phenylalanine	261**
(261)	N-(3,5-dichlorobenzenesulfonyl)-(L)-5- methylprolyl-(L)-4-fluorophenylalanine	520
(262)	N-(3,5-dichlorobenzenesulfonyl)-3- phenylazetidiny carbonyl-(L)-4- fluorophenylalanine	568

(263)	N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-allylprolyl-(L)-4-fluorophenylalanine	529
(264)	N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methylprolyl-(L)-phenylalanine	
(265)	N-(3-trifluoromethylbenzenesulfonyl)-(L)-2(S)-methylprolyl-(L)-4-nitro-phenylalanine	530
(266)	N-(3,5-dichlorobenzenesulfonyl)-(L)-3(R)-methylprolyl-(L)-4-fluorophenylalanine	502.3
(267)	N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methylprolyl-(L)-4-cyanophenylalanine	509
(268)	N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methylprolyl-(L)-4-(aminocarbonyl)-phenylalanine	545
(269)	N-(3,5-dichlorobenzenesulfonyl)-(L)-3(R)-methylprolyl-(L)-4-(N-t-butoxycarbonylaminomethyl)-phenylalanine	631.4
(270)	N-(3,5-dichlorobenzenesulfonyl)-(L)-3(R)-methylprolyl-(L)-4-(aminomethyl)-phenylalanine	514.3

* m/e: (M + 1 (H⁺))⁺ or (M + 18 (NH₄⁺))⁺

** (M - 159: N/SO₂Ar cleavage)

EXAMPLE 271

5

N-(3-Trifluoromethylphenylsulfonyl)-(L)- 2(S)-methyl-prolyl-(L)-4-acetaminophenylalanine.

Step A: N-(3-trifluoromethylphenylsulfonyl)-(L)- 2(S)-methyl-prolyl-(L)-4-aminophenylalanine, methyl ester.

To a solution of N-(3-trifluoromethylphenylsulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-nitrophenylalanine, methyl ester (0.45 g, 0.85 mmol; prepared according to the methodology described in Example 225) in methanol (40 mL) was added 10% palladium on carbon catalyst (50 mg) and the resulting black suspension was stirred under 1 atm of hydrogen for 45 min. The reaction mixture was filtered (Whatman

syringless filter device) and rotoevaporated under high vacuum to an off-white solid (0.42 g, 99% yield) which was used in the following step without further purification.

¹H-NMR (400 MHz, CDCl₃): δ 8.12 (s, 1H), 8.05 (d, 1H, J = 7.8 Hz),
5 7.81 (d, 1H, J = 7.7 Hz), 7.64 (t, 1H, J = ~7.9 Hz), 7.03 (d, 1H, J = 7.6 Hz),
6.97 (d, 2H, J = 8.4 Hz), 6.73 (d, 2H, J = 8.4), 4.76 (m, 1H), 3.75 (s, 3H), 3.48
(m, 1H), 3.28 (m, 1H), 3.14 (dd, 1H, J = 14.2, 5.4 Hz), 2.98 (dd, 1H, J = 14.2,
6.9 Hz), 2.29 (m, 1H), 1.78 (m, 1H), 1.62 (m, 2H), 1.57 (s, 3H).

10 Step B: N-(3-trifluoromethylphenylsulfonyl)-(L)- 2(S)-methyl-prolyl-
(L)-4-acetaminophenylalanine, methyl ester

To a solution of N-(3-trifluoromethylphenylsulfonyl)-(L)-
2(S)-methyl-prolyl-(L)-4-aminophenylalanine, methyl ester (42 mg, 0.082
mmol) in dry dichloromethane (0.5 mL) at 0 °C, was added successively
15 2,6-lutidine (0.03 mL, 0.25 mmol; 3.0 equiv), acetyl chloride (0.01 mL,
0.125 mmol; 1.5 equiv), and 4-dimethylaminopyridine (10 mg, 0.082
mmol; 1.0 equiv). The yellow reaction mixture was stirred overnight.
After this time, 1.0 N hydrochloric acid was added followed by extraction
with ethyl acetate (3x). The combined organic layer was successively
20 washed with saturated sodium bicarbonate solution and saturated salt
solution and dried over anhydrous magnesium sulfate. The mixture
was filtered and concentrated to furnish an orange-yellow oil (46 mg,
100% crude yield) which was purified by preparative thin layer
chromatography (80% ethyl acetate, 20% hexanes). Yield: 39 mg (85%).

25 ¹H-NMR (400 MHz, CDCl₃): δ 8.11 (s, 1H), 8.04 (d, 1H, J = 8.0 Hz),
7.82 (d, 1H, J = 7.7 Hz), 7.64 (t, 1H, J = ~7.9 Hz), 7.41 (d, 1H, J = 8.4 Hz),
7.25 (s, 1H), 7.09 (d, 2H, J = 8.4 Hz), 7.07 (d, 1H, J = ~8.0 Hz), 4.80 (m, 1H),
3.75 (s, 3H), 3.49 (m, 1H), 3.24 (m, 2H), 3.04 (dd, 1H, J = ~14.0, ~7.0 Hz),
2.29 (m, 1H), 2.13 (s, 3H), 1.75 (m, 1H), 1.61 (m, 2H), 1.57 (s, 3H).

30

Step C: N-(3-trifluoromethylphenylsulfonyl)-(L)- 2(S)-methyl-prolyl-
(L)-4-acetaminophenylalanine.

To a solution of N-(3-trifluoromethyl)-2(S)-methyl-propyl-4-acetamino-(S)-phenylalanine, methyl ester (33 mg, 0.059 mmol) in ethanol (1.0 mL) was added 0.2 N sodium hydroxide solution (0.60 mL, 0.12 mmol; 2.0 equiv). The reaction mixture was stirred overnight (15 h) and then acidified with 1.0 N hydrochloric acid and extracted with ethyl acetate (3x). The combined organic layer was washed with saturated salt solution, dried over anhydrous magnesium sulfate, and rotoevaporated to yield an off-white solid (31 mg, 97% yield).

MS: m/e 542 (M+H⁺); 559 (M+NH₄⁺).

¹H-NMR (400 MHz, CD₃OD): δ 8.08 (m, 2H), 7.95 (d, 1H, J = 7.7 Hz), 7.76 (t, 1H, J = ~7.9 Hz), 7.48 (m, 3H), 7.18 (d, 2H, J = 8.4), 4.69 (m, 1H), 3.43 (m, 1H), 3.32 (m, 2H), 3.05 (dd, 1H, J = ~14.0, ~7.0 Hz), 2.12 (m, 1H), 2.08 (s, 3H), 1.71 (m, 3H), 1.56 (s, 3H).

The following compounds were prepared by the procedures described in Example 271 using the acyl or sulfonyl chloride or alkyl or aryl isocyanate:

Ex.	Compound Name	MS *
(272)	N-(3-trifluoromethylphenylsulfonyl)-(L)-2(S)-methyl-propyl-(L)-4-(N'-(2-toluy)ureido)phenylalanine.	633
(273)	N-(3-trifluoromethylphenylsulfonyl)-(L)-2(S)-methyl-propyl-(L)-4-(N'-(4'-fluorophenylsulfonyl)ureido)phenylalanine.	718
(274)	N-(3-trifluoromethylphenylsulfonyl)-(L)-2(S)-methyl-propyl-(L)-4-(ethoxycarbonyl)aminophenylalanine.	572
(275)	N-(3-trifluoromethylphenylsulfonyl)-(L)-2(S)-methyl-propyl-(L)-4-(4'-(N'-(2-toluy)ureido)phenylacetyl)aminophenylalanine.	766

(276)	N-(3-trifluoromethylphenylsulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(4'-fluorophenylsulfonyl)aminophenylalanine.	658
(277)	N-(3-trifluoromethylphenylsulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(phenylacetyl)aminophenylalanine.	618
(278)	N-(3-trifluoromethylphenylsulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(4'-fluorobenzoyl)aminophenylalanine.	622
(279)	N-(3-trifluoromethylphenylsulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(isobutyloxycarbonyl)aminophenylalanine.	600
(280)	N-(3-trifluoromethylphenylsulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-methylsulfonylaminophenylalanine.	578
(281)	N-(3-trifluoromethylphenylsulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(N'-(4-fluorophenyl)ureido)phenylalanine.	637
(282)	N-(3-trifluoromethylbenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(N-(1,1-dioxo-1,2-isothiazolidinyl)-phenylalanine	621
(283)	N-(3-trifluoromethylphenylsulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(N'-(4-(2-oxo-1-pyrrolidinyl)-phenylalanine.	585

* m/e: (M + 1 (H⁺))⁺ or (M + 18 (NH₄⁺))⁺

EXAMPLE 284

5 N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(4'-fluorobenzoyl)phenylalanine

Step A: 4-Iodo-(L)-Phenylalanine, tert-butyl ester hydrochloride.

To a suspension of N-Boc-4-iodo-(L)-phenylalanine (1.0 g, 2.56 mmol) in methylene chloride (7 mL) and cyclohexane (14 mL) were added t-butyl trichloroacetimidate (0.48 mL, 2.68 mmol) and boron trifluoride-etherate (48 μ L). The reaction mixture was stirred for 5 hours at room temperature under a nitrogen atmosphere and then treated a second time with the same amounts of t-butyl trichloroacetimidate and boron trifluoride-etherate as above. After stirring overnight, a third addition was made, and the mixture was stirred a further 3 hours. The mixture was then filtered and the filtrate evaporated. The product was obtained pure by silica gel chromatography eluting with 10% diethyl ether in hexane; yield 650 mg. The product was treated with 1M HCl in ethyl acetate (7.3 mL) for 18 hours at room temperature. The mixture was evaporated and coevaporated several times with diethyl ether to afford the title compound; yield 522 mg.

400 MHz ^1H NMR (CD_3OD): δ 1.42 (s, 9H); 3.13 (d, 2H); 4.18 (t, 1H); 7.09 (d, 2H); 7.75 (d, 2H).

Step B: N-(3,5-Dichlorobenzenesulfonyl)-(L)-proline

To a mixture of (L)-proline methyl ester hydrochloride (838 mg, 5.06 mmol) in methylene chloride (25 mL) at 0°C were added N,N-diisopropylethylamine (2.64 mL, 15.2 mmol) and a solution of 3,5-dichlorobenzenesulfonyl chloride (1.49 g, 6.07 mmol) in methylene chloride (5 mL). The cooling bath was removed, and the mixture was stirred overnight at room temperature. It was then diluted with methylene chloride, washed with 1N hydrochloric acid, saturated NaHCO_3 , saturated brine solution, dried over anhydrous sodium sulfate, and evaporated. The methyl ester was obtained pure by silica gel chromatography eluting with 10% acetone in hexane; yield 1.49 g. It was then taken up in ethanol (50 mL) and treated with 0.2 N sodium hydroxide (26.6 mL) for 1.5 hours at room temperature. The mixture was acidified with glacial acetic acid, concentrated, the residue taken up in methylene chloride, washed with water, saturated brine solution, dried (Na_2SO_4), and evaporated to give the title compound; yield 1.4 g.

400 MHz ^1H NMR (CD_3OD): δ 1.80-2.15 (m, 4H); 3.35-4.45 (m, 2H); 4.30 (dd, 1H); 7.76 (m, 1H); 7.83 (m, 2H).

Step C: N-(3,5-Dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-iodophenylalanine, tert-butyl ester.

To a solution of N-(3,5-dichlorobenzenesulfonyl)-(L)-proline (386 mg, 1.19 mmol) in methylene chloride (23 mL) were added 1-hydroxybenzotriazole (241 mg, 1.79 mmol), N-methylmorpholine (0.33 mL, 2.98 mmol), and 4-iodo-(L)-phenylalanine tert-butyl ester hydrochloride (458 mg, 1.19 mmol). After cooling in an ice-bath for 5 minutes, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (274 mg, 1.43 mmol) was added. After 15 minutes, the cooling bath was removed, and the mixture was stirred overnight under a nitrogen atmosphere. The mixture was diluted with methylene chloride, washed with water, 1N HCl, saturated NaHCO_3 solution, saturated brine solution, dried (Anhydrous magnesium sulfate), and evaporated. Silica gel chromatography eluting with 20% ethyl acetate in hexane afforded pure title compound; yield 651 mg (84%).

MS: m/e 653 ($M + 1$)

400 MHz ^1H NMR (CD_3OD): δ 1.45 (s, 9H); 1.65-1.85 (m, 4H); 3.0 (dd, 1H); 3.13 (dd, 1H); 3.45 (m, 1H); 4.20 (m, 1H); 4.55 (dd, 1H); 7.05 (d, 2H); 7.64 (d, 2H); 7.80 (s, 3H).

Step D: N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(4'-fluorobenzoyl)phenylalanine, tert-butyl ester.

A solution of N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-4-iodo-(L)-phenylalanine tert-butyl ester (100 mg, 0.15 mmol), 4-fluorobenzeneboronic acid (23 mg, 0.16 mmol), potassium carbonate (62 mg, 0.45 mmol), bis(triphenylphosphine)-palladium(II) chloride (4 mg, 0.0057 mmol) in anisole (4 mL) was flushed with nitrogen, then flushed with CO, and a balloon of CO was attached. The solution was then stirred at 80°C for 5 hours on a timer overnight. The following day the solution was diluted with methylene chloride, washed once with water,

once with brine, dried over Anhydrous magnesium sulfate, and solvent removed in vacuo. The desired product was obtained by silica gel chromatography eluting with methylene chloride, followed by 10% ethyl acetate in methylene chloride; yield 70 mg (72%)

- 5 MS: m/e 666.2 (M+H+NH₃)
 400 MHz ¹H NMR (CD₃OD): δ 1.46(s,9H); 1.65-1.95(m,4H); 3.05-3.15 (dd,1H); 3.47(m,1H); 4.2(dd,1H); 4.65(m,1H); 7.20(t,2H); 7.45(d,2H); 7.70(d,2H);7.76-7.85(m,5H)

10 Step E: N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(4'-fluorobenzoyl)phenylalanine

- A solution of N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(4-fluorobenzoyl)phenylalanine, tert-butyl ester (23 mg, 0.035 mmol) in methylene chloride(1.2 mL) was cooled in ice bath. Trifluoroacetic acid
 15 (0.167 mL, 2.17 mmol) was then added, and ice bath was removed and reaction mixture was allowed to stir overnight at room temperature. The reaction mixture was then evaporated, coevaporated with methylene chloride(2X), toluene(2X), and methanol(2X). The product was obtained
 20 pure by eluting with 20% ethyl acetate in methylene chloride, followed by 8% methanol in methylene chloride; yield 19 mg(91%)

MS: m/e 609.8(M+H+NH₃)
 400 Mhz ¹H NMR (CD₃OD): δ 1.6-1.95(m,4H): 3.1-3.45(m,4H): 4.17 (dd,1H): 4.55(m,1H): 7.2(t,2H): 7.4(d,2H): 7.66(d,2H): 7.78-7.85(m,5H)

- 25 The following compounds were prepared by the procedures described in Example 284 using the appropriate arylboronic acid derivative in Step D:

Ex.	Compound Name	MS *
(285)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4'-(2-methoxybenzoyl)phenylalanine	604.8

(286) N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl- 624
prolyl-(L)-4-(4'-fluorobenzoyl)phenylalanine

* m/e: (M + 1 (H⁺))⁺ or (M + 18 (NH₄⁺))⁺

EXAMPLE 287

5 N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(4-fluorobenzyl)phenyl
alanine

Step A: N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-
(4-fluoro- α -hydroxybenzyl)phenylalanine, tert-butyl ester.

10 A solution of N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-
(4'-fluorobenzoyl)phenylalanine (38 mg) in methanol (5 mL) was cooled
to 0° C. Sodium borohydride (3 mg) was added. After stirring for 20 min,
the solvent was removed by rotoevaporation and the residue dissolved in
15 dichloromethane (30 mL). The solution was successively washed with
water and saturated salt solution and dried over anhydrous magnesium
sulfate. The mixture was filtered and the solvent was removed by
rotoevaporation. The title compound (38 mg) was recovered and used
with no further purification in the subsequent reaction.

20 Step B: N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-
(4-fluorobenzyl)phenylalanine

A solution of N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-
(4-fluorophenyl-hydroxymethyl)phenylalanine, tert-butyl ester (38 mg)
and triethylsilane (21 μ L) in anhydrous dichloromethane was flushed
25 with dry nitrogen for five minutes. The solution was then cooled in an
ice bath and boron trifluoride etherate (16 μ L) was added. After stirring
for 3 hours, methanol (1 mL) was added and the solvent was removed by
rotoevaporation. The residue was dissolved in ethyl acetate and the
solution successively washed with saturated sodium bicarbonate
30 solution and saturated salt solution and then dried over anhydrous
magnesium sulfate. After the mixture was filtered, the solvent was

removed by rotoevaporation. The residue was purified by flash column chromatography on silica gel eluted with 97.75% dichloromethane, 2% methanol and 0.25% acetic acid to yield the title compound (14 mg).

M/S: $m/e = 597.2 (M + NH_4)$.

- 5 1H NMR (400 MHz, CD_3OD): δ 1.5-1.7 (m, 2H), 1.75-1.82 (m, 2H), 2.95-3.05 (m, 1H), 3.2-3.4 (m, 3H), 3.88 (s, 2H), 4.1-4.2 (m, 1H), 4.6-4.7 (m, 1H), 6.90 (t, $J = 9$, 2H), 7.1-7.22 (m, 6H), 7.72 (s, 2H), 7.76 (s, 1H).

- 10 The following compounds were prepared by the procedures described in Example 287:

Ex.	Compound Name	MS *
(288)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(2-methoxybenzyl)phenylalanine	608.3
* m/e : $(M + 1 (H^+))^+$ or $(M + 18 (NH_4^+))^+$		

15 EXAMPLE 289

N-(3,5-Dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(2-nitrophenoxy)-phenylalanine

- 20 Step A: N-Boc-4-(2-nitrophenoxy)-(L)-phenylalanine, methyl ester
 To a solution of N-Boc-(L)-tyrosine, methyl ester (500 mg) and potassium carbonate (467 mg) in dimethylformamide (5 mL) was added dropwise 1-fluoro-2-nitrobenzene (189 μ L). The yellow solution was stirred for 3 days at room temperature. The mixture was diluted
 25 with ether which was subsequently washed with 1N hydrochloric acid, water, saturated salt solution and dried over anhydrous magnesium sulfate. After filtration, the solvent was removed by rotoevaporation to yield the title compound (700 mg) which was used in the subsequent reaction without further purification.

¹H NMR (400 MHz, CD₃OD): δ 1.38 (s, 9H), 3.85-3.15 (m, 2 H), 4.3-4.4(m, 1H), 6.95-7.1 (m, 3H), 7.24-7.3(m, 3H), 7.55-7.61 (t, 1H), 7.97-7.97(m, 1H).

Step B: 4-(2-nitrophenoxy)-(L)-phenylalanine, methyl ester
5 hydrochloride

N-Boc-4-(2-nitrophenoxy)-(L)-phenylalanine, methyl ester (600 mg) was stirred in a solution of 1N hydrochloric acid in ethyl acetate (10 mL) for 18 hours at room temperature. A precipitate formed, the solvent was removed by rotoevaporation, and co-evaporated with Et₂O (2x). The
10 solid was than suspended with ethyl acetate, filtered, washed with diethyl ether, and allowed to air dry. The title compound was recovered (490 mg) and used in the subsequent reaction without further purification.

15 Step C: N-(3,5-Dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(2-nitrophenoxy)phenylalanine, methyl ester.

A solution of N-(3,5-dichlorobenzenesulfonyl)-(L)-proline (429 mg), 4-(2-nitrophenoxy)-(L)-phenylalanine, methyl ester hydrochloride (445 mg), 1-hydroxybenzotriazole (255 mg), N-methylmorpholine (0.35 mL)
20 in dichloromethane (32 mL) was cooled to 0 °C. 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC; 289 mg) was then added. The reaction was allowed to warm to room temperature and stirred for 17 hr. The reaction was diluted with dichloromethane (100 mL) and successively washed with water, 1N
25 hydrochloric acid, saturated sodium bicarbonate solution, and saturated salt solution. The organic layer was dried over anhydrous magnesium sulfate. The solution was filtered and the solvent removed by rotoevaporation. The residue was purified by flash column chromatography on silica gel eluted with 20% ethyl acetate in hexane to
30 afford the title compound (714 mg) which was used in the subsequent reaction.

Step D: N-(3,5-Dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(2-nitrophenoxy)-phenylalanine

N-(3,5-Dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(2-nitrophenoxy)-phenylalanine, methyl ester (110 mg) was dissolved in ethanol (6 mL) and a solution of potassium hydroxide (15 mg) in water (2 mL) was added. After stirring for 20 minutes, the reaction was acidified with acetic acid and the solvent removed by rotoevaporation. The residue was dissolved in ethyl acetate (40 mL), and the solution successively washed with saturated sodium bicarbonate solution and saturated salt solution. The solution was dried over anhydrous magnesium sulfate, then filtered and the solvent removed by rotoevaporation to afford the title compound (40 mg).

M/S: m/e 625(M+NH₄)⁺.

¹H NMR (400 MHz, CD₃OD): δ 1.63-1.72(m, 1H), 1.75-2.92(m, 3H), 3.01-3.08(dd, 1H), 3.25-3.35(m, 2H), 3.4-3.5 (m, 1H), 4.19 (dd, J= 6,1, 1H), 4.68-4.74 (m, 1H), 6.97-7.05 (m, 3H), 7.2-7.35 (m, 3H), 7.45-7.5 (m, 1H), 7.77 (s, 3H), 7.91 (dd, J= 7,2, 1H).

The following compound was prepared by the procedures described in Example 289:

Example	Compound Name	MS*
(290)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(4-nitrophenoxy)-phenylalanine	625
(291)	N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(2-nitrophenoxy)-phenylalanine	639

* m/e: (M + 1 (H⁺))⁺ or (M + 18 (NH₄⁺))⁺

25

EXAMPLE 292

N-(3,5-Dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(2-aminophenoxy)-phenylalanine

Step A: N-(3,5-Dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(2-aminophenoxy)-phenylalanine, methyl ester

To a solution of N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(2-nitro-phenoxy)-phenylalanine, methyl ester (120 mg) in ethanol (4.5 mL) was added iron filings (42 mg) and acetic acid (0.5 mL). Reaction was refluxed for 3 h then cooled to room temperature. The mixture was filtered through a pad of celite and the solvent was removed by rotoevaporation. The resultant tar was dissolved in ethyl acetate and successively washed with saturated sodium bicarbonate solution and saturated salt solution. The organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent removed by rotoevaporation. The residue was purified by flash column chromatography on silica gel eluted with 40% ethyl acetate in hexane to afford N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(2-aminophenoxy)-phenylalanine, methyl ester (75 mg) which was used in the subsequent reaction.

Step B: N-(3,5-Dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(2-aminophenoxy)-phenylalanine

N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(2-aminophenoxy)-phenylalanine, methyl ester was hydrolyzed by the procedure in Example 289, step D to afford N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(2-aminophenoxy)-phenylalanine.

M/S: m/e 578(M+1).

¹H NMR (400 MHz, CD₃OD): δ 1.62-1.9 (m, 4H), 3.0-3.07 (dd, 1H), 3.2-3.3(m, 2H), 3.4-3.5 (m, 1H), 4.19 (t, 1H), 4.62-4.7 (m, 1H), 6.6-6.65 (m, 1H), 6.73-6.77 (dd, 1H), 6.85-6.95 (m, 4H), 7.2 (d, J=2, 2H), 7.78 (s, 3H), 8.1-8.15 (d, 1H).

EXAMPLE 293

N-(3,5-Dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(2-acetylamino-phenoxy)-phenylalanine

Step A: N-(3,5-Dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(2-acetylamino-phenoxy)-phenylalanine, methyl ester

To a solution of N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(2-amino-phenoxy)-phenylalanine, methyl ester (55 mg) in pyridine (0.31 mL) and dichloromethane (4 mL) was dropwise added acetic anhydride (0.16 mL). After stirring for 1 hr, the reaction was diluted with dichloromethane (50 mL) and successively washed with water and saturated salt solution. The solution was dried over anhydrous magnesium sulfate, filtered and the solvent removed by rotoevaporation. The residue was purified by flash column chromatography on silica gel eluted with 5% ethyl acetate in dichloromethane to afford N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(2-acetylamino-phenoxy)-phenylalanine, methyl ester (41 mg) which was used in the subsequent reaction.

Step B: N-(3,5-Dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(2-acetylamino-phenoxy)-phenylalanine

N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(2-acetylamino-phenoxy)-phenylalanine, methyl ester was hydrolyzed by the procedure in Example 289, step D to afford N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(2-acetylamino-phenoxy)-phenylalanine.

M/S: m/e 637(M+NH₄)⁺.

¹H NMR (400 MHz, CD₃OD): δ 1.6-1.95 (m, 4H), 2.06 (s, 3H), 3.0-3.08 (dd, 1H), 3.2-3.3 (m, 2H), 3.4-3.48 (m, 1H), 4.15-4.2 (m, 1H), 5.55-5.61 (m, 1H), 6.8-6.85 (d, 1H), 6.91 (d, J= 9, 2H), 6.98-7.08 (m, 2H), 7.26 (d, J=9, 2H), 7.78 (s, 3H), 8.85-8.90 (dd, 1H).

The following compounds were prepared by the procedures described in Example 293:

Ex.	Compound Name	MS*
(294)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(4-acetylaminophenoxy)-phenylalanine	637
(295)	N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methylprolyl-(L)-4-(2-acetylaminophenoxy)-phenylalanine	636

* m/e: (M + 1 (H⁺))⁺ or (M + 18 (NH₄⁺))⁺

5

EXAMPLE 296N-(3,5-Dichlorobenzenesulfonyl)-2-(S)-methyl-(L)-prolyl-4-(2-cyanophenoxy)-phenylalanine

10 Step A: N-Boc-4-(2-cyanophenoxy)-phenylalanine, methyl ester

A solution of 500 mg of N-Boc-4-(L)-tyrosine, methyl ester, 205 mg 2-fluorobenzonitrile, 245 mg KF 40 wt% on alumina, 45 mg 18-crown-6, and 7 mL of acetonitrile was run at reflux for seven days. The reaction was then diluted with methylene chloride, and washed with

15 water and saturated salt solution. The organic layers were then dried over anhydrous magnesium sulfate and the solvent was removed in vacuo. The product was purified via silica gel chromatography eluted with 80% hexane:20% acetone to yield 253 mg of the product.

20 ¹H NMR (400 Mhz, CD₃OD): δ 1.38(s, 9H), 2.9(dd, 1H), 3.13(dd, 1H), 3.70(s, 3H), 3.38(m, 1H), 6.88(d, 1H), 7.03 (d, J=9, 2H), 7.2(t, 1H), 7.29(d, J=9, 2H), 7.55(t, 1H), 7.72,(d, 1H).

Step B: 4-(2-cyanophenoxy)-phenylalanine, methyl ester,hydrochloride

25 The reaction was performed by an analogous procedure as described in Example 289, step B to yield the title compound.

Step C: N-Boc-2-(S)-methyl-(L)-prolyl-4-(2-cyanophenoxy)-phenylalanine, methyl ester

To a solution of 131 mg of N-Boc-2-(S)-methyl-(L)-proline, 190 mg 4-(2-cyanophenoxy)-phenylalanine, methyl ester hydrochloride, 297 mg PyBOP, and 4 mL of methylene chloride at 0° C was added 300 uL of diisopropylethylamine via syringe. The reactants were allowed to warm to room temperature and said reaction was run over the weekend. The reaction was then diluted with methylene chloride, washed with water, 1N hydrochloric acid, saturated sodium bicarbonate solution, and saturated salt solution. The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo. The product was purified via silica gel chromatography, eluted with 80% hexane:20% acetone to yield 263 mg of the title compound.

Step D: N-Boc-2-(S)-methyl-(L)-prolyl-4-(2-cyanophenoxy)-phenylalanine, methyl ester hydrochloride

The reaction was performed by an analogous procedure as described in Example 289, step B to yield the title compound.

Step E: N-(3,5-Dichlorobenzenesulfonyl)-2-(S)-methyl-(L)-prolyl-4-(2-cyanophenoxy)-phenylalanine, methyl ester

To a solution of 95 mg of N-Boc-2-(S)-methyl-(L)-prolyl-4-(2-cyanophenoxy)-phenylalanine, hydrochloride, 61 mg 3,5-dichlorobenzenesulfonyl chloride, and 2.5 mL of tetrahydrofuran at 0° C was added 110 uL of diisopropylethylamine via syringe. The reaction was allowed to warm to room temperature and run at said temperature overnight. The reaction was diluted with methylene chloride, washed with water, 1N hydrochloric acid, saturated sodium bicarbonate solution, and saturated salt solution.. The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo. The product was purified via silica gel chromatography, eluted with 80% hexane:20% acetone to yield 62 mg of N-(3,5-dichlorobenzenesulfonyl)-2-(S)-methyl-(L)-prolyl-4-(2-cyanophenoxy)-phenylalanine, methyl ester.

Step F: N-(3,5-Dichlorobenzenesulfonyl)-2-(S)-methyl-(L)-prolyl- 4-(2-cyanophenoxy)-phenylalanine

To a solution of 62 mg of N-(3,5-dichlorobenzenesulfonyl)-2-(S)-methyl-(L)-prolyl-4-(2-cyanophenoxy)-phenylalanine, methyl ester in 5 mL of ethanol was added a solution of 11 mg potassium hydroxide in 2 mL of water. After 1.5 hours the solvent was removed in vacuo. The resultant solid was then dissolve in methylene chloride and washed with 0.5 M hydrochloric acid and saturated salt solution. The organic layers were dried over anhydrous magnesium sulfate and concentrated in vacuo. The formed diastereomers were separated via HPLC using a YMC ODS-AQ column, eluting with 80% MeOH: 20% WATER + 0.1% TFA. The faster eluting product was shown to be the desired product. M/S: m/e 619 (M+1+NH₃).

¹H NMR (400 Mhz, CD₃OD): δ 1.60(s, 3H), 1.7-1.9(m, 3H), 2.12-2.21(m, 1H), 3.08-3.16(dd, 1H), 3.3-3.5(m), 4.65-4.75(m, 1H), 6.91(d, J=8 1H), 7.04(d, 2H), 7.15 (t, 1H), 7.36 (d, J=9, 2H), 7.4-7.5 (t, 1H), 7.6-7.8(m, 4H).

The following compound was prepared by the procedures described in Example 296:

Ex.	Compound Name	MS*
(297)	N-(3,5-Dichlorobenzenesulfonyl)-2-(S)-methyl-(L)-prolyl-4-(4-cyanophenoxy)-phenylalanine	619

25

EXAMPLE 298

N-(3,5-Dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine.

Step A: N-(3,5-Dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine, methyl ester.

To a solution of 3,5-dichlorobenzenesulfonyl-(L)-proline (from Example 284, Step B) (1.70 gm, 5.23 mmole) in dry dichloromethane (15 mL) was added 1-hydroxybenzotriazole hydrate (782.3 mg, 5.78 mmole) followed by N-methylmorpholine (1.45mL, 13.1 mmole), (L)-O-tert-butyl-tyrosine, methyl ester hydrochloride (1.58 gm, 6.31 mmole), and 1-ethyl-3-(3-dimethylamino-propyl) carbodiimide (1.41 gm, 7.36 mmole). Additional dichloromethane (5 mL) was added and the solution stirred under nitrogen at 25°C overnight. Water was added and the layers separated. The aqueous layer was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were successively washed with water (2 x 20 mL) and saturated salt solution and dried over anhydrous magnesium sulfate. After filtration, the solvent was removed by rotoevaporation. The residue was purified by flash column chromatography on silica gel eluted with 5-35% ethyl acetate in hexanes to yield N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine, methyl ester as a pale white foam (2.85 gm, 98% yield).

MS: m/e 557.4 (M+1)⁺.
400 MHz ¹H NMR (CD₃OD): δ 1.28 (s, 9H), 1.49-1.66 (m, 3H), 2.03-2.07 (m, 1H), 2.99 (dd, J = 14.0, 7.5 Hz, 1H), 3.06-3.12 (m, 1H), 3.19 (dd, J = 14.1, 5.5 Hz, 1H), 3.34-3.39 (m, 1H), 3.74 (s, 3H), 4.04-4.07 (m, 1H), 4.76-4.81 (m, 1H), 6.88 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 8.4 Hz, 3H), 7.58 (t, J = 1.8 Hz, 1H), 7.69 (d, J = 1.8 Hz, 2H).

25 Step B: N-(3,5-Dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine.

Under a dry nitrogen atmosphere, to a solution of 1.20gm (2.15 mmole) of N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine, methyl ester (1.20 gm, 2.15 mmole) in dry ethanol (25.8mL) was added dropwise an aqueous 0.2N sodium hydroxide solution (12.9mL, 2.58 mmole). The reaction was stirred for 1.5 hr at room temperature. A 1.0M aqueous solution of acetic acid (~2 mL) was added until pH 4-5 was obtained. The solvent was removed by

rotoevaporation and the residue dissolved in dichloromethane and water. The layers were separated and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The organic layers were combined, and successively washed with water, saturated salt
5 solution, and dried over anhydrous sodium sulfate. After filtration, the solvent was removed by rotoevaporation. The residue dissolved in a minimum of dichloromethane and purified on a 4000 μ m silica gel plate on a Chromatotron, eluted with 1-10% methanol in
10 dichloromethane to yield N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine as a pale yellow foam (1.15 gm, 99% yield).
MS: m/e 543.3 (M+1)⁺.
400 MHz NMR (CD₃OD) δ 1.28 (s, 9H), 1.60-1.69 (m, 1H), 1.70-1.79 (m, 1H), 1.82-1.89 (m, 2H), 3.02-3.06 (m, 1H), 3.21-3.30 (m, 4H), 3.41-3.49 (m, 1H), 4.19 (br t, J = 6.60 Hz, 1H), 4.62 (br s, 1H), 6.90 (d, J = 8.3 Hz,
15 2H), 7.18 (d, J = 8.4 Hz, 2H), 7.78 (s, 3H).

EXAMPLE 299

20 N-(3,5-Dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-methyl-tyrosine.

Step A: N-(3,5-Dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine, tert-butyl ester

By the procedure of Example 284, step C, N-(3,5-dichlorobenzenesulfonyl)-(L)-proline was coupled with (L)-O-tert-butyl-tyrosine, tert-butyl ester hydrochloride. The product was
25 purified by flash column chromatography on silica gel eluted with 5-35% ethyl acetate in hexane and isolated as a white foam (85% yield).

MS: m/e 599.0 (M+1)⁺.
30 400 Mhz ¹H NMR (CDCl₃) δ 1.28 (s, 9H), 1.42 (s, 9H), 1.56-1.63 (m, 4H), 2.05-2.08 (m, 1H), 2.99 (dd, J = 14.0, 6.7 Hz, 1H), 3.09-3.17 (m, 2H), 3.35-3.38 (m, 1H), 4.06-4.08 (m, 1H), 4.67 (br dd, J = 14.0, 6.3 Hz, 1H), 6.87

(br d, $J = 8.5$ Hz, 2H), 7.03 (br d, $J = 8.4$ Hz, 3H), 7.06 (br d, $J = 7.6$ Hz, 1H), 7.57 (t, $J = 1.8$ Hz, 1H), 7.70 (d, $J = 1.8$ Hz, 2H).

Step B: N-(3,5-Dichlorobenzenesulfonyl)-(L)-prolyl-(L)-tyrosine, tert-butyl ester

To a solution of N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine, tert-butyl ester (1.20 gm, 2.00 mmole) in dry dichloromethane (6 mL) at 0° C under a dry nitrogen atmosphere was dropwise added a 50% v/v solution of trifluoroacetic acid in dichloromethane (3.08 mL, 20 mmol) over a 10 min period. After stirring for 2 hr, the reaction mixture was quenched at 0° C with an aqueous 5% sodium bicarbonate solution to pH = 7-8. The layers were separated and the organic layer dried over anhydrous magnesium sulfate. After filtration, the solvent was removed by rotoevaporation and the residue purified by flash column chromatography on silica gel eluted with 1-10% methanol in dichloromethane to yield N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-tyrosine, tert-butyl ester as a white foam (1.71 gm, 78% yield). MS: m/s 543.4 ($M+1$)⁺.
400 MHz ¹H NMR (CDCl₃) δ 1.45 (s, 9H), 1.55-1.63 (m, 3H), 2.07 (m, 1H), 2.94 (dd, $J = 14.1, 6.90$ Hz, 1H), 3.09-3.16 (m, 2H), 3.37-3.39 (m, 1H), 4.06-4.09 (m, 1H), 4.65-4.70 (m, 1H), 6.71 (d, $J = 8.5$ Hz, 2H), 7.01 (d, $J = 8.5$ Hz, 2H), 7.06 (d, $J = 7.7$ Hz, 1H), 7.58 (t, $J = 1.8$ Hz, 1H), 7.70 (d, $J = 1.8$ Hz, 2H).

Step C: N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-methyl-tyrosine, tert-butyl ester

To a solution of N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-tyrosine, tert-butyl ester (100 mg, 0.184 mmole) dissolved in dry dimethylformamide (1.0 mL) was added anhydrous potassium carbonate (76.3 mg, 0.552 mmol) and iodomethane (52.3 mg, 0.736 mmole). The reaction mixture was stirred vigorously at 25° C overnight under a dry nitrogen atmosphere. Ethyl acetate (30 mL)

was added and the solution acidified with aqueous 5% citric acid to pH = 5. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). Organic layers were combined and washed successively with water and saturated salt solution, and dried over anhydrous magnesium sulfate. After filtration, the solvent was removed by rotoevaporation and the residue dissolved in a minimum of dichloromethane. This solution was loaded onto a 1000 micron silica gel Chromatotron plate and purified by gradient elution with 10-50% ethyl acetate in hexane to afford N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-methyl-tyrosine, tert-butyl ester as an off-white powder (76 mg, 74% yield).

MS: m/e 557.5 (M+1)⁺.

400 MHz ¹H-NMR (CDCl₃) δ 1.44 (s, 9H), 1.56-1.69 (m, 3H), 2.08-2.11 (m, 1H), 2.95 (dd, J = 14.0, 6.68 Hz, 1H), 3.09-3.16 (m, 2H), 3.35-3.40 (m, 1H), 3.75 (s, 3H), 4.07-4.09 (m, 1H), 4.66 (dd, J = 13.8, 6.4 Hz, 1H), 6.78 (d, J = 8.4 Hz, 2H), 7.04 (d, J = 8.6 Hz, 3H), 7.57 (t, J = 1.8 Hz, 1H), 7.70 (d, J = 1.8 Hz, 2H).

Step D: N-(3,5-Dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-methyl-tyrosine.

To a solution of N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-methyl-tyrosine, tert-butyl ester (50 mg, 0.090 mmole) dissolved in dry dichloromethane (0.3 mL) and anisole (5 μL) at 0°C under a dry nitrogen atmosphere was dropwise added a 50% v/v solution of trifluoroacetic acid in dichloromethane (276 μL, 1.8 mmole). After the addition was completed, the ice bath was removed, and the reaction mixture allowed to stir vigorously for 2.5 hr. The reaction mixture was treated with dichloromethane (20 mL) and 5% aqueous sodium bicarbonate to pH = 5. After separation of phases, the aqueous layer was extracted with dichloromethane (2 x 10 mL). The organic layers were combined and successively washed with water and saturated salt solution. The solution was dried over anhydrous magnesium sulfate and filtered. The solvent was

removed by rotoevaporation and the residue dissolved in a minimum of dichloromethane. This solution was loaded onto a 1000 micron silica gel plate on a Chromatotron eluted with 1-10% methanol in dichloromethane to afford N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-methyl-tyrosine as a light brown powder (28.5 mg, 63% yield).

MS: m/e 501.2 (M+1)⁺.

400 MHz ¹H-NMR (CD₃OD) δ 1.56-1.65 (m, 2H), 1.74-1.85 (m, 1H), 1.86-1.88 (m, 1H), 3.01 (dd, J = 13.9, 6.4 Hz, 1H), 3.16-3.24 (m, 2H), 3.37-3.43 (m, 1H), 3.72 (s, 3H), 4.12 (dd, J = 8.5, 3.4 Hz, 1H), 4.45 (br t, J = 5.7 Hz, 1H), 6.79 (d, J = 8.6 Hz, 2H), 7.15 (d, J = 8.6 Hz, 2H), 7.80 (br m, 3H).

The following compounds were prepared by the procedures described in Example 299 using the appropriate alkylating or acylating agent in Step C:

15

Ex.	Compound Name	MS *
(300)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-benzyl-tyrosine	577.4
(301)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-n-butyl-tyrosine	543.5
(302)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-cyanomethyl-tyrosine	526.4
(303)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-(2-methoxyethyl)-tyrosine	547.4
(304)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-(2-ethoxyethyl)-tyrosine	559.4
(305)	N-(benzenesulfonyl)-(L)-prolyl-(L)-O-(2-methoxyethyl)-tyrosine	477.0
(306)	N-(benzenesulfonyl)-(L)-prolyl-(L)-O-(2-ethoxyethyl)-tyrosine	491.2
(307)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-(1-pyrrolidinylcarbonyl)-tyrosine	584.3

(308)	N-(benzenesulfonyl)-(L)-prolyl-(L)-O-(1-pyrrolidinylcarbonyl)-tyrosine	516.3
(309)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-(tert-butyl acetate)-tyrosine	618
(310)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-(4-morpholinyl-carbonyl)-tyrosine	599.1
(311)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-(1-(2-propanonyl)-tyrosine	543.3
(312)	N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-O-(1-pyrrolidinylcarbonyl)-tyrosine	598
(313)	N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-O-(tert-butyl acetate)-tyrosine	632.1
(314)	N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-O-(2-ethoxyethyl)-tyrosine	559.3
(315)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-(acetic acid)-tyrosine, methyl ester	559.4
(316)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-(acetic acid)-tyrosine	545.2
(317)	N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-O-(1-(2-propanonyl)-tyrosine	557.3
(318)	N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-O-(1-pyrrolidinylcarbonyl)-tyrosine, methyl ester	612.4
(319)	N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-O-(4-morpholinyl-carbonyl)-tyrosine	614.2
(320)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-(2-pyrrolylcarbonyl)-tyrosine	580.3
(321)	N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-O-(N-phenyl-N-methylaminocarbonyl)-tyrosine	634.4
(322)	N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-O-(N,N-diethyl-aminocarbonyl)-tyrosine	600.3

(323)	N-(3-chlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-O-(4-morpholinyl-carbonyl)-tyrosine	580.3
(324)	N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-O-(N,N-diisopropyl-aminocarbonyl)-tyrosine	628.6
(325)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-(benzoyl)-tyrosine	591.3
(326)	N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-(cyclopentanoyl)-tyrosine	583.3

* m/e: (M + 1 (H⁺))⁺ or (M + 18 (NH₄⁺))⁺

EXAMPLE 327

5 N-(3,5-Dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-(5-tetrazolyl)methyl-tyrosine

Step A: N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-cyanomethyl-tyrosine, tert-butyl ester

- 10 To a solution of N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-tyrosine, tert-butyl ester (200 mg, 0.368 mmole, obtained from Example 299, Step A) dissolved in 2.0 mL of dry dimethylformamide was added bromoacetonitrile (353.1 mg, 2.94 mmole) and anhydrous potassium carbonate (152.6 mg, 1.10 mmole).
- 15 The reaction mixture was stirred vigorously under a dry nitrogen atmosphere at 40°C overnight. The reaction mixture was then diluted with ethyl acetate and acidified with 5% aqueous citric acid to pH = 5. After separation of the organic layers, the aqueous layer was washed with fresh ethyl acetate (3X). The combined organic layers
- 20 were successively washed with water, saturated salt solution, and then dried over anhydrous magnesium sulfate. The residue obtained after filtration and removal of solvents was purified on a 1000 micron Chromatotron plate by gradient elution using 10-8-5-4-2-1:1

Hexane:EtoAc. This afforded 150.4 mg (70% yield) of the title compound as an off-white powder.

MS.: (ESI) m/e 582.4 (M+1)⁺.

¹H-NMR 400 MHz (CDCl₃) δ 1.44 (s, 9H), 1.56-1.69 (m, 3H), 2.08-2.11 (m, 1H), 3.00 (dd, J = 14.0, 6.68 Hz, 1H), 3.05-3.13 (m, 1H), 3.21 (dd, J = 14.0, 6.69 Hz, 1H), 3.35-3.51 (m, 1H), 4.09 (dd, J = 8.5, 3.4 Hz, 1H), 4.68 (dd, J = 13.8, 6.4 Hz, 1H), 4.73 (s, 2H), 6.89 (d, J = 8.7 Hz, 2H), 7.09 (d, J = 8.6 Hz, 2H), 7.15 (d, J = 8.7 Hz, 2H), 7.58 (distorted m, 1H), 7.70-7.73 (distorted m, 2H).

Step B: N-(3,5-Dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-(5-tetrazolyl)methyl-tyrosine, tert-butyl ester

A mixture of N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-cyanomethyl-tyrosine, tert-butyl ester (82.0 mg, 0.141 mmol) and f trimethyltin azide (101.4 mg, 0.493 mmol) in 6 mL of dry toluene was stirred at reflux for 1 day. The reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was treated with 6 mL of dry methanol and 3 g of silica gel and stirred vigorously overnight at room temperature. This slurry was concentrated to give a powder. This was vacuum-dried and then added as a slurry in methylene chloride to a 4.0 x 7.0 cm cartridge of Flash-40 silica gel and eluted with 10% methanol in methylene chloride. The fractions containing the desired product were combined and concentrated to yield 33.0 mg (38.2% yield) of the titled compound as a white powder.

Mass spectrum (ESI) m/e 630.1 (M+18)⁺.

¹H-NMR 400 MHz (CD₃OD) δ 1.41 (s, 9H), 1.61-1.92 (m, 3H), 2.08-2.11 (m, 1H), 2.97-3.01 (distorted m, 1H), 3.09 (dd, J = 14.0, 6.2 Hz, 1H), 3.24-3.28 (m, 1H), 3.39-3.46 (m, 1H), 4.17-4.21 (m, 1H), 4.52 (dd, J = 14.0, 5.9 Hz, 1H), 5.37 (s, 2H), 6.99 (d, J = 8.7 Hz, 2H), 7.18 (d, J = 8.7 Hz, 2H), 7.78-7.80 (distorted m, 3H), 8.15 (d, J = 8.1 Hz, 1H).

Step C: N-(3,5-Dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-

(5-tetrazolyl)methyl-tyrosine

- A mixture of N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-(5-tetrazolyl)methyl-tyrosine, tert-butyl ester (30 mg, 0.0489 mmol) was dissolved in 2 mL of dry methylene chloride and was cooled in an ice bath. A solution of 1/1 v/v of trifluoroacetic acid (55.7 mg, 0.489 mmol) and methylene was added, which was stirred vigorously for three hr ice temperature. A stream of dry nitrogen was applied to remove the solvents and the residue was loaded onto a reverse phase prep-plate (RP-18wF₂₅₄s 0.2 mm 20 x 20 cm, EM Science) using a minimal amount of methylene chloride and eluted with 40:60 water/acetonitrile. The product band was collected and extracted with 10% methanol/methylene chloride, concentrated to provide 5.0 mg (18% yield) of the titled compound as a white foam material.
- Mass spectrum (ESI) m/e 569.3 (M+1)⁺.
¹H-NMR 500 MHz (CD₃OD) δ 1.61-1.87 (m, 3H), 2.05 (distorted m, 1H), 3.02 (dd, J = 14.0, 8.1 Hz, 1H), 3.18 (dd, J = 14.1, 5.2 Hz, 1H), 3.23-3.28 (m, 1H), 3.39-3.43 (m, 1H), 4.22 (t, J = 6.0 Hz, 1H), 4.64 (dd, J = 8.0, 5.3 Hz, 1H), 5.41 (s, 2H), 6.99 (distorted d, J = 2.1 Hz, 2H), 7.22 (distorted d, J = 1.8 Hz, 2H), 7.76-7.78 (m, 3H).

EXAMPLE 328

N-(3,5-Dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-N^ε-benzyl-histidine

- Step A: N-t-Butyloxycarbonyl-(L)-2(S)-methyl-proline
2(S)-Methyl-proline (4.98 g, 38.55 mmol) was dissolved in dioxane (40 mL) and water (40 mL) to give a suspension. Triethyl amine (11.4 gm, 46.27 mmol) was added, followed by the addition of 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile (BOC-ON, 5.85 gm, 57.83 mmol). The reaction mixture was stirred at room temperature overnight to give a yellow solution. The reaction was

quenched with water (150 mL) and diethyl ether (225 mL). The organic layers were separated and the ether layer extracted with water (80 mL). The combined aqueous layers were cooled to 0°C and treated with 2N hydrochloric acid to pH = 2, and then extracted with ethyl acetate (3 x 150 mL). The combined organic layers were dried with over anhydrous sodium sulfate, filtered and concentrated to yield 7.24 g (82% yield) of the titled compound as a white solid (mp = 119-125°C).

Mass spectrum (ESI) m/e 230.1 (M+1)⁺.

¹H-NMR 400 MHz (CD₃OD) δ 1.41 (s, 9H), 1.49 (s, 3H), 1.85-1.99 (m, 3H), 2.13-2.25 (m, 1H), 3.43-3.54 (m, 2H).

Step B: N-t-Butyloxycarbonyl-(L)-2(S)-methyl-prolyl-(L)-N^ε-benzyl-histidine, methyl ester.

A mixture of N-t-butyloxycarbonyl-(L)-2(S)-methyl-proline (300 mg, 1.31 mmol) and of (L)-N^ε-benzyl-histidine, methyl ester dihydrochloride (339.28 mg, 1.31 mmol) in dry dimethylformamide (5 mL) and methylene chloride (2.5 mL) was stirred at room temperature. Diisopropylethyl amine (684.6 μL, 3.93 mmol) was added followed by the addition of benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphosphate hexafluorophosphate (PyBOP, 681.6 mg, 1.31 mmol) and the mixture was stirred overnight. This reaction mixture was treated with 2N hydrochloric acid, water, and ethyl acetate. The layers were separated and the aqueous layer was extracted with ethyl acetate (3X). The combined organic layers were washed with saturated sodium bicarbonate, water, saturated salt solution and dried over anhydrous magnesium sulfate. After filtration and removal of solvent by rotoevaporation, the residue was purified by flash chromatography on silica gel and eluted with 10-9-8-7-6-5-4-3-2-1:1 Hexane:ethyl acetate and finally with 1-2% methanol/methylene chloride. The fractions containing the desired material were

combined and concentrated to yield 357.8 mg (58% yield) of the titled compound as a sticky white foam.

Mass spectrum (ESI) m/e 471.5 (M+1)⁺.

- 400 MHz (CD₃OD) δ 1.34 (s, 9H), 1.43 (distorted s, 3H), 1.62-2.05 (m, 4H), 2.98-3.11 (m, 2H), 3.38-3.42 (m, 1H), 3.47-3.55 (m, 1H), 3.66 (s, 3H), 4.66-4.70 (m, 1H), 5.16 (distorted s, 2H), 6.95 (s, 1H), 7.26-7.38 (m, 5H), 7.86 (s, 1H), 8.09 (s, 1H).

Step C: (L)-2(S)-Methyl-prolyl-(L)-N^c-

- 10 benzyl-histidine, methyl ester, dihydrochloride.

A mixture of N-t-butyloxycarbonyl-(L)-2(S)-methyl-prolyl-(L)-N-benzyl-histidine, methyl ester (272.5 mg, 0.649 mmol) and hydrochloric acid_(g)/ethyl acetate (14.0 mL, 58.4 mmol) in dry ethyl acetate (2 mL) was stirred at room temperature for one hour.

- 15 Methylene chloride was added and solvents were removed by rotoevaporation. The residue was dried under high vacuum overnight and gave 235.1 mg (97.6% yield) of the titled compound.

Mass spectrum (CI) m/e 371.3 (M+1)⁺.

- ¹H-NMR 400 MHz (CD₃OD) δ 1.43 (s, 3H), 1.87-1.93 (m, 1H), 2.01-2.13 (m, 2H), 2.32-2.37 (m, 1H), 3.14-3.21 (m, 1H), 3.29-3.38 (m, 4H), 3.71 (s, 3H), 4.77 (dd, J = 10.1, 5.3 Hz, 1H), 5.39 (s, 2H), 7.40-7.43 (m, 5H), 9.05 (distorted s, 1H).

Step D: N-(3,5-Dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-N^c-benzyl-histidine, methyl ester.

- 25 (L)-2(S)-methyl-prolyl-(L)-N-benzyl-histidine, methyl ester, dihydrochloride (191.3 mg, 0.516 mmol) was dissolved in dry tetrahydrofuran (5 mL) and dry dimethylformamide (2.5 mL). Diisopropylethyl amine (269.8 μL, 1.55 mmol) and 4, 4'-
30 dimethylaminopyridine were added to this solution. After cooling to 5°C for 5 minutes, a solution of 3,5-dichlorobenzenesulfonyl chloride (190.2 mg, 0.774 mmol) in dry tetrahydrofuran (2.5 mL) was added to the reaction mixture which was allowed to reach room temperature

overnight. This reaction mixture was treated with water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (3X). The organic layers were combined and successively washed with water and saturated salt solution and dried with anhydrous magnesium sulfate. After filtration, the solvents were removed by rotoevaporation. The residue was purified on a 4.0 x 7.0 cm cartridge of Flash-40 silica gel and eluted 1-2-3-4-5% methanol/methylene chloride to yield 116.6 mg (39% yield) of the titled compound.

Mass spectrum (CI) m/e 579.1 (M+1)⁺.

¹H-NMR 400 MHz (CDCl₃) δ 1.67 (s, 3H), 1.72-1.86 (m, 2H), 1.91-1.98 (m, 1H), 2.30-2.35 (m, 1H), 3.12 (dd, J = 15.0, 4.76 Hz, 1H), 3.18 (dd, J = 14.6, 6.02 Hz, 1H), 3.33-3.39 (m, 1H), 3.66 (s, 3H), 4.77 (dd, J = 6.11, 1.27 Hz, 1H), 5.04 (s, 2H), 6.76 (s, 1H), 7.12-7.15 (m, 2H), 7.29-7.35 (m, 3H), 7.72 (distorted d, J = 1.99 Hz, 2H), 7.99 (distorted s, 2H).

Step E: N-(3,5-Dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-N^ε-benzyl-histidine.

A mixture of N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-N-benzyl-histidine, methyl ester (115.5 mg, 0.199 mmol) in 0.2N sodium hydroxide in ethanol (1.2 mL) was stirred at room temperature for 4 hours. The reaction mixture was treated with ethyl acetate and 5% citric acid to pH = 3-4. The aqueous layer was extracted with ethyl acetate (3X). The combined organic layers were washed with saturated salt solution and dried over anhydrous magnesium sulfate. The solution was filtered and the solvents were removed by rotoevaporation. The residue was purified on a 4.0 x 7.0 cm cartridge of Flash-40 silica gel eluted with 15% methanol/methylene chloride to yield 51.2 mg (45.5% yield) of the titled compound as a light brown foam.

Mass spectrum (ESI) m/e 565.4 (M+1)⁺.

¹H-NMR 400 MHz (CDCl₃) δ 1.28 (s, 3H), 1.75-1.84 (m, 3H), 2.10-2.14 (m, 1H), 3.06-3.12 (m, 1H), 3.24-3.29 (m, 2H), 3.31-3.42 (m, 2H), 4.46-

4.49 (m, 1H), 5.23 (s, 2H), 7.18 (s, 1H), 7.30-7.37 (m, 5H), 7.74-7.79 (m, 3H), 8.34 (broad s, 1H).

EXAMPLE 329

5

N-Benzenesulfonyl-(L)-prolyl-2-amino-2-norbornanecarboxylic acid

Step A: 2-Amino-2-norbornanecarboxylic acid, methyl ester hydrochloride.

10 To 25 mL of methanol at 0 °C was added thionyl chloride (2.4 mL, 32 mmol). After stirring at 0 °C for 5 min, 2-amino-2-norbornanecarboxylic acid (1.0 g, 6.4 mmol) was added in one portion, and the mixture was heated at reflux for 16 h. The mixture was concentrated to give the product (1.2 g, 92%) as a white solid.

15

Step B: N-Benzenesulfonyl-(L)-prolyl-2-amino-2-norbornanecarboxylic acid, methyl ester

To a solution of 2-amino-2-norbornanecarboxylate, methyl ester hydrochloride (400 mg, 2.0 mmol), N-benzenesulfonyl-(L)-proline (510 mg, 2.0 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (306 mg, 2.0 mmol), 1-hydroxybenzotriazole (202 mg, 2.0 mmol) in 4 mL of tetrahydrofuran at 0 °C was added N-methyl morpholine (0.22 mL, 2.0 mmol). After 15 min at 0 °C, the reaction mixture was stirred at room temperature for 16 h, and was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluted with 10:1 methylene chloride/ethyl acetate to give the title compound (478 mg, 59%) as a mixture of diastereomers.

25

MS: calculated for C₂₀H₂₆N₂O₅S 406; found m/e 417 (M+H⁺), 423 (M+NH₄⁺).

30

Step C: N-Benzenesulfonyl-(L)-prolyl-2-amino-2-norbornanecarboxylic acid

A solution of N-phenylsulfonyl-(L)-prolyl-2-amino-2-norbornanecarboxylic acid, methyl ester (210 mg, 0.2 mmol) in 3 mL of 1:1 aqueous sodium hydroxide (1 M) and methanol was stirred at room temperature for 2 weeks. The reaction was quenched with concentrated hydrochloric acid (0.2 mL), and the resulting mixture was partitioned between saturated salt solution and ethyl acetate. The product was extracted with ethyl acetate and was purified by flash chromatography on silica gel eluted with 100:5:1 methylene chloride/methanol/acetic acid to give the product as a mixture of diastereomers.

MS: calculated for C₁₉H₂₄N₂O₅S, 392; found m/e 393 (M+H⁺), 410 (M+NH₄⁺)

EXAMPLE 330

N-Benzenesulfonyl-(L)-prolyl-3(R)-methyl-phenylalanine

Step A: N-Benzenesulfonyl-(L)-prolyl-3(R)-methyl-phenylalanine, methyl ester.

The title compound was prepared by the procedure described in Example 289 Steps A - C starting from (L)-3(R)-methyl-phenylalanine (prepared by the procedure of Hruby and coworkers: Tetrahedron, 1992, 48, 4733).

Step B: N-Benzenesulfonyl-(L)-prolyl-3(R)-methyl-phenylalanine.

A solution of N-phenylsulfonyl-(L)-prolyl-(L)-3(R)-methyl-phenylalanine, methyl ester (23 mg, 0.053 mmol) in 1.0 mL of 1:1 tetrahydrofuran/water at 0 °C was added lithium hydroxide hydrate (12 mg, 0.033 mmol) and hydrogen peroxide (30%, 33 mL, 0.033 mmol). The reaction was allowed to warm up to 18 °C over 2 hr. The reaction was quenched with dilute sodium thiosulfate and 1 M hydrochloric acid, and the resulting mixture was partitioned between

saturated salt solution and ethyl acetate. The product was extracted with ethyl acetate and purified by flash column chromatography on silica gel eluted with 50:50:1 ethyl acetate/hexane/acetic acid to 20:1 ethyl acetate/acetic acid to give the product (17 mg, 77%).

5 MS: calculated for C₂₁H₂₄N₂O₅S, 416; found m/e 417 (M+H⁺), 434 (M+NH₄⁺)

¹H-NMR (500 Mhz, CD₃OD) δ 8.2-7.2 (10H, m), 4.65 (1H, d), 4.23 (1H, dd), 3.48-3.36 (2H, m), 3.23 (1H, m), 2.0-1.2 (4H, m), 1.38 (3H, d)

10

EXAMPLE 331

N-Phenylsulfonyl-(L)-prolyl-(L)-2,3-methano-phenylalanine and N-Phenylsulfonyl-(L)-prolyl-(D)-2,3-methano-phenylalanine.

15 Step A: N-Phenylsulfonyl-(L)-prolyl-(L)-2,3-methano-phenylalanine, methyl ester and N-Phenylsulfonyl-(L)-prolyl-(D)-2,3-methano-phenylalanine, methyl ester.

The title compounds were prepared by the procedure described in Example 289, Steps A-C starting from E-2,3-methanophenylalanine, methyl ester hydrochloride (prepared by the
20 procedure of Stammers and coworkers: J. Org. Chem., 1982, 47, 3270). Under the described conditions, reaction of diazomethane with Z-2-phenyl-4-benzylidene-5-oxazolinone (Aldrich) gave a 4:1 mixture of Z-1,5-diphenyl-6-oxa-4-azaspiro(2,4)hept-4-ene-7-one and E-1,5-diphenyl-6-oxa-4-azaspiro(2,4)hept-4-ene-7-one, and the minor
25 diastereomer was carried on to E-2,3-methanophenylalanine methyl ester hydrogen chloride salt as described. Subsequent peptide coupling (51 mg scale) afforded a 1:1 mixture of diastereomers, which were partially separated on silica gel eluting with 4:4:1 methylene
30 chloride/hexane/ethyl acetate.

Top isomer: ¹H-NMR (500 Mhz, CD₃OD) δ 8.0-7.1 (10 H, m), 4.18 (1H, dd), 3.60 (1H, ddd), 3.30 (3 H, S), 3.4-3.2 (1H, m), 2.96 (1 H, dd), 2.18 (1H, dd), 2.1-1.8 (3H, m), 1.7-1.6 (1H, m), 1.58 (1H, dd)

Bottom isomer: $^1\text{H-NMR}$ (500 Mhz, CD_3OD) δ 8.0-7.2 (10 H, m), 4.24 (1H, dd), 3.66 (1 H, ddd), 3.30 (3 H, S), 3.26 (1H, ddd), 2.88 (1 H, dd), 2.22 (1H, dd), 2.1-1.8 (3H, m), 1.66-1.60 (1H, m), 1.53 (1H, dd)

5 Step B: N-Phenylsulfonyl-(L)-prolyl-(L)-2,3-methano-phenylalanine and N-phenylsulfonyl-(L)-prolyl-(D)-2,3-methano-phenylalanine.

To a solution of the top isomer of N-phenylsulfonyl-(L)-prolyl-2,3-methanophenylalanine, methyl ester (15 mg, 0.035 mmol)
10 in 0.6 mL of 1:1 tetrahydrofuran/water was added lithium hydroxide hydrate (15 mg, 0.35 mmol), and the mixture was stirred at room temperature for 15 hr. The reaction was quenched with concentrated hydrochloric acid (0.2 mL), and the resulting mixture was
15 partitioned between brine and ethyl acetate. The product was extracted with ethyl acetate and was purified by flash chromatography on silica gel eluted with 100:5:1 methylene chloride/methanol/acetic acid to give the product in quantitative yield. MS: calculated for $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_5\text{S}$, 414; found m/e 415.3 ($\text{M}+\text{H}^+$), 432.3 ($\text{M}+\text{NH}_4^+$)
20 $^1\text{H-NMR}$ (500 Mhz, CD_3OD) δ 8.0-7.0 (10 H, m), 4.10 (1H, dd), 3.60 (1H, ddd), 3.27 (1H, ddd), 2.84 (1 H, dd), 2.18 (1H, dd), 2.1-1.8 (3H, m), 1.66-1.56 (1H, m), 1.57 (1H, dd).

The bottom isomer was hydrolyzed in the same fashion
25 as described for the top isomer:

MS: calculated for $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_5\text{S}$, 414; found m/e 415.2 ($\text{M}+\text{H}^+$), 432.2 ($\text{M}+\text{NH}_4^+$)

$^1\text{H-NMR}$ (500 Mhz, CD_3OD) δ 8.0-7.1 (10H, m), 4.06 (1H, dd), 3.66 (1 H, ddd), 3.27 (1H, ddd), 2.86 (1 H, dd), 2.19 (1H, dd), 2.1-1.8 (3H, m),
30 1.68-1.58 (1H, m), 1.52 (1H, dd).

EXAMPLE 332

N-(3,5-Dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(5-((1H,3H)-1,3-dimethylpyrimidine-2,4-dione))-phenylalanine

- Step A: N-(3-Fluorobenzenesulfonyl)-(L)-prolyl-(L)-4-trimethylstannylphenylalanine, tert-butyl ester.

A solution of N-(3-fluorobenzenesulfonyl)-(L)-prolyl-(L)-4-iodophenylalanine, tert-butyl ester (1.0 gm, 1.53 mmol), hexamethylditin (411 μ L, 2.14 mmol), triphenylphosphine (8 mg, 0.03 mmol), lithium chloride (71 mg, 1.68 mmol), and tetrakis(triphenylphosphine)palladium(0) (88 mg, 0.077 mmol) in 1,4-dioxane (10 mL) was heated to 95°C under a dry nitrogen atmosphere for 1.5 hr. The solution was cooled and diluted with ethyl acetate (100 mL) and successively washed with 1N sodium hydroxide solution (2X) and saturated salt solution (1X). After drying over anhydrous magnesium sulfate, the solution was filtered and the solvent removed by rotoevaporation. The residue was purified by silica gel column chromatography eluted with 10% acetone in hexanes to yield N-(3-fluorobenzenesulfonyl)-(L)-prolyl-(L)-4-(trimethylstannyl)phenylalanine, tert-butyl ester (577 mg, 54% yield). MS: m/e 658 (M + 18; NH₄⁺).

N-(3,5-Dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-trimethylstannylphenylalanine, tert-butyl ester was prepared from N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-iodophenylalanine, tert-butyl ester by an analogous procedure.

Step B: N-(3,5-Dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(5-((1H,3H)-1,3-dimethylpyrimidine-2,4-dione))-phenylalanine, tert butyl ester

A solution of N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-trimethylstannylphenylalanine, tert-butyl ester (70 mg, 0.1 mmol), (1H,3H)-1,3-dimethyl-5-iodo-pyrimidine-2,4-dione (40 mg, 0.15 mmol) and tetrakis-triphenylphosphine palladium (4

mg, 0.003 mmol) in dry dimethylformamide (1 mL) was heated in an oil bath at 100°C for 1 hr under a dry nitrogen atmosphere. After cooling, the solvent was removed by rotoevaporation under high vacuum. The residue was purified by flash column chromatography on silica gel eluted with 15% acetone in hexanes to give the title compound as a light yellow solid (27 mg, 40% yield).
MS: (m/e) 696 (M + 18 (NH₄⁺)).

Step C: N-(3,5-Dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(5-((1H,3H)-1,3-dimethylpyrimidine-2,4-dione))phenylalanine

The tert-butyl ester of N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(5-((1H,3H)-1,3-dimethylpyrimidine-2,4-dione))-phenylalanine, tert butyl ester (24 mg, 0.035 mmol) was stirred in a solution of trifluoroacetic acid (170 µL, 2.2 mmol) in methylene chloride (1.0 mL) according to the procedure described in Example 225, Step E to yield the title compound.
MS: (m/e) 640 (M + 18 (NH₄⁺)).

EXAMPLE 333

20

Inhibition of VLA-4 Dependent Adhesion to BSA-CS-1 Conjugate

Step A. Preparation of CS-1 Coated Plates.

Untreated 96 well polystyrene flat bottom plates were coated with bovine serum albumin (BSA; 20 µg/ml) for 2 hours at room temperature and washed twice with phosphate buffered saline (PBS). The albumin coating was next derivatized with 10 µg/ml 3-(2-pyridyldithio) propionic acid N-hydroxysuccinimide ester (SPDP), a heterobifunctional crosslinker, for 30 minutes at room temperature and washed twice with PBS. The CS-1 peptide (Cys-Leu-His-Gly-Pro-Glu-Ile-Leu-Asp-Val-Pro-Ser-Thr), which was synthesized by conventional solid phase chemistry and purified by reverse phase HPLC, was next added to the derivatized BSA at a concentration of 2.5 µg/ml and allowed to react

for 2 hours at room temperature. The plates were washed twice with PBS and stored at 4°C.

Step B. Preparation of Fluorescently Labeled Jurkat Cells.

5 Jurkat cells, clone E6-1, obtained from the American Type Culture Collection (Rockville, MD; cat # ATCC TIB-152) were grown and maintained in RPMI-1640 culture medium containing 10% fetal calf serum (FCS), 50 units/ml penicillin, 50 µg/ml streptomycin and 2 mM glutamine. Fluorescence activated cell sorter analysis with specific
10 monoclonal antibodies confirmed that the cells expressed both the α4 and β1 chains of VLA-4. The cells were centrifuged at 400xg for five minutes and washed twice with PBS. The cells were incubated at a concentration of 2×10^6 cells/ml in PBS containing a 1 µM concentration of a fluorogenic esterase substrate (2', 7'-bis-(2-carboxyethyl)-5-(and -6)-carboxyfluorescein, acetoxymethyl ester; BCECF-AM; Molecular Probes
15 Inc., Eugene, Oregon; catalog #B-1150) for 30-60 minutes at 37°C in a 5% CO₂/air incubator. The fluorescently labeled Jurkat cells were washed two times in PBS and resuspended in RPMI containing 0.25% BSA at a final concentration of 2.0×10^6 cells/ml.

20

Step C. Assay Procedure.

Compounds of this invention were prepared in DMSO at 100x the desired final assay concentration. Final concentrations were selected from a range between 0.001 nM-100 µM. Three µL of diluted
25 compound, or vehicle alone, were premixed with 300 µL of cell suspension in 96-well polystyrene plates with round bottom wells. 100 µL aliquots of the cell /compound mixture were then transferred in duplicate to CS-1 coated wells. The cells were next incubated for 30 minutes at room temperature. The non-adherent cells were removed by
30 two gentle washings with PBS. The remaining adherent cells were quantitated by reading the plates on a Cytofluor II fluorescence plate reader (Perseptive Biosystems Inc., Framingham, MA; excitation and emission filter settings were 485 nm and 530 nm, respectively). Control

wells containing vehicle alone were used to determine the level of cell adhesion corresponding to 0% inhibition. Control wells coated with BSA and crosslinker (no CS-1 peptide) were used to determine the level of cell adhesion corresponding to 100% inhibition. Cell adhesion to wells coated with BSA and crosslinker was usually less than 5% of that observed to CS-1 coated wells in the presence of vehicle. Percent inhibition was then calculated for each test well and the IC_{50} was determined from a ten point titration using a validated four parameter fit algorithm.

10

EXAMPLE 334

Antagonism of VLA-4 Dependent Binding to VCAM-Ig Fusion Protein.

Step A. Preparation of VCAM-Ig.

15

The signal peptide as well as domains 1 and 2 of human VCAM (GenBank Accession no. M30257) were amplified by PCR using the human VCAM cDNA (R & D Systems) as template and the following primer sequences: 3'-PCR primer: 5'-AATTATAATTTGATCAACTTAC CTGTCAATTCTTTTACAGCCTGCC-3';

20

5'-PCR primer:

5'-ATAGGAATTCCAGCTGCCACCATGCCTGGGAAGATGGTCG-3'.

The 5'-PCR primer contained EcoRI and PvuII restriction sites followed by a Kozak consensus sequence (CCACC) proximal to the initiator methionine ATG. The 3'-PCR primer contained a BclI site and a splice donor sequence. PCR was performed for 30 cycles using the following parameters: 1 min. at 94°C, 2 min. at 55°C, and 2 min. at 72°C. The amplified region encoded the following sequence of human VCAM-1:

MPGKMVVILGASNILWIMFAASQAFKIETTPESRYLAQIGDSVSLTC
STTGCESPFFSWRTQIDSPLNGKVTNEGTTSTLTMPVSVFGNEHSYLC
TATCESRKLEKGIQVEIYSFPKDPEIHLSGPLEAGKPITVKCSVADVY
PFDRLEIDLLKGDHLMKSQEFLEDADRKSLETKSLEVTFTFVIEDIGKV
LVCRAKLHIDEMDSVPTVRQAVKEL. The resulting PCR product of

650 bp was digested with EcoRI and BclI and ligated to expression vector pIg-Tail (R & D Systems, Minneapolis, MN) digested with EcoRI and BamHI. The pIg-Tail vector contains the genomic fragment which encodes the hinge region, CH2 and CH3 of human IgG1 (GenBank
5 Accession no. Z17370). The DNA sequence of the resulting VCAM fragment was verified using Sequenase (US Biochemical, Cleveland, OH). The fragment encoding the entire VCAM-Ig fusion was subsequently excised from pIg-Tail with EcoRI and NotI and ligated to pCI-neo (Promega, Madison, WI) digested with EcoRI and NotI. The
10 resulting vector, designated pCI-neo/VCAM-Ig was transfected into CHO-K1 (ATCC CCL 61) cells using calcium-phosphate DNA precipitation (Specialty Media, Lavallete, NJ). Stable VCAM-Ig producing clones were selected according to standard protocols using 0.2-0.8 mg/ml active G418 (Gibco, Grand Island, NY), expanded, and cell
15 supernatants were screened for their ability to mediate Jurkat adhesion to wells previously coated with 1.5 µg/ml (total protein) goat anti-human IgG (Sigma, St. Louis, MO). A positive CHO-K1/VCAM-Ig clone was subsequently adapted to CHO-SFM serum-free media (Gibco) and maintained under selection for stable expression of VCAM-Ig. VCAM-
20 Ig was purified from crude culture supernatants by affinity chromatography on Protein A/G Sepharose (Pierce, Rockford, IL) according to the manufacturer's instructions and desalted into 50 mM sodium phosphate buffer, pH 7.6, by ultrafiltration on a YM-30 membrane (Amicon, Beverly, MA).

25

Step B. Preparation of ¹²⁵I-VCAM-Ig.

VCAM-Ig was labeled to a specific radioactivity greater than 1000 Ci/mmol with ¹²⁵I-Bolton Hunter reagent (New England Nuclear, Boston, MA; cat # NEX120-0142) according to the manufacturer's
30 instructions. The labeled protein was separated from unincorporated isotope by means of a calibrated HPLC gel filtration column (G2000SW; 7.5 x 600 mm; Tosoh, Japan) using uv and radiometric detection.

Step C. VCAM-Ig Binding Assay.

Compounds of this invention were prepared in DMSO at 100x the desired final assay concentration. Final concentrations were selected from a range between 0.001 nM-100 μ M. Jurkat cells were centrifuged at 400xg for five minutes and resuspended in binding buffer (25 mM HEPES, 150 mM NaCl, 3 mM KCl, 2 mM glucose, 0.1% bovine serum albumin, pH 7.4). The cells were centrifuged again and resuspended in binding buffer supplemented with MnCl_2 at a final concentration of 1 mM. Compounds were assayed in Millipore MHVB multiscreen plates (cat# MHVBN4550, Millipore Corp., MA) by making the following additions to duplicate wells: (i) 200 μ L of binding buffer containing 1 mM MnCl_2 ; (ii) 20 μ L of ^{125}I -VCAM-Ig in binding buffer containing 1 mM MnCl_2 (final assay concentration ~ 100 pM); (iii) 2.5 μ L of compound solution or DMSO; (iv) and 0.5×10^6 cells in a volume of 30 μ L. The plates were incubated at room temperature for 30 minutes, filtered on a vacuum box, and washed on the same apparatus by the addition of 100 μ L of binding buffer containing 1 mM MnCl_2 . After insertion of the multiscreen plates into adapter plates (Packard, Meriden, CT, cat# 6005178), 100 μ L of Microscint-20 (Packard cat# 6013621) was added to each well. The plates were then sealed, placed on a shaker for 30 seconds, and counted on a Topcount microplate scintillation counter (Packard). Control wells containing DMSO alone were used to determine the level of VCAM-Ig binding corresponding to 0% inhibition. Control wells in which cells were omitted were used to determine the level of binding corresponding to 100% inhibition. Binding of ^{125}I -VCAM-Ig in the absence of cells was usually less than 5% of that observed using cells in the presence of vehicle. Percent inhibition was then calculated for each test well and the IC_{50} was determined from a ten point titration using a validated four parameter fit algorithm.

EXAMPLE 335

Antagonism of $\alpha_4\beta_7$ Dependent Binding to VCAM-Ig Fusion Protein.

Step A. $\alpha_4\beta_7$ Cell line.

RPMI-8866 cells (a human B cell line $\alpha_4^+\beta_1^-\beta_7^+$; a gift from Prof. John Wilkins, University of Manitoba, Canada) were grown in
5 RPMI/10% fetal calf serum/ 100 U penicillin/100 μ g streptomycin/2 mM L-glutamine at 37°C, 5 % carbon dioxide. The cells were pelleted at 1000 rpm for 5 minutes and then washed twice and resuspended in binding buffer (25 mM Hepes, 150 mM NaCl, 0.1 % BSA, 3 mM KCl, 2 mM Glucose, pH 7.4).

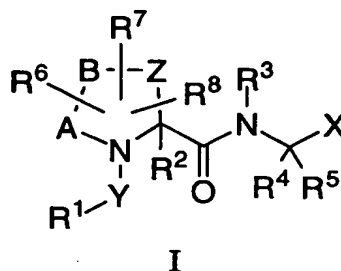
10

Step B. VCAM-Ig Binding Assay.

Compounds of this invention were prepared in DMSO at 100x the desired final assay concentration. Final concentrations were selected from a range between 0.001 nM-100 μ M. Compounds were
15 assayed in Millipore MHVB multiscreen plates (Cat# MHVBN4550) by making the following sequential additions to duplicate wells: (i) 100 μ L/well of binding buffer containing 1.5 mM MnCl_2 ; (ii) 10 μ L/well ^{125}I -VCAM-Ig in binding buffer (final assay concentration < 500 pM); (iii) 1.5 μ L/well test compound or DMSO alone; (iv) 38 μ L/well RPMI-8866 cell
20 suspension (1.25×10^6 cells/well). The plates were incubated at room temperature for 45 minutes on a plate shaker at 200 rpm, filtered on a vacuum box, and washed on the same apparatus by the addition of 100 μ L of binding buffer containing 1 mM MnCl_2 . After insertion of the multiscreen plates into adapter plates (Packard, Meriden, CT, cat#
25 6005178), 100 μ L of Microscint-20 (Packard cat# 6013621) was added to each well. The plates were then sealed, placed on a shaker for 30 seconds, and counted on a Topcount microplate scintillation counter (Packard). Control wells containing DMSO alone were used to determine the level of VCAM-Ig binding corresponding to 0% inhibition.
30 Wells in which cells were omitted were used to determine the level of binding corresponding to 100% inhibition. Percent inhibition was then calculated for each test well and the IC_{50} was determined from a ten point titration using a validated four parameter fit algorithm.

WHAT IS CLAIMED IS:

1. A method for the treatment of diseases, disorders, conditions or symptoms mediated by cell adhesion in a mammal which comprises administering to said mammal an effective amount of a compound Formula I:



10

or a pharmaceutically acceptable salt thereof wherein:

- R¹ is
- 1) C₁-10alkyl,
 - 2) C₂-10alkenyl,
 - 3) C₂-10alkynyl,
 - 4) Cy,
 - 5) Cy-C₁-10alkyl,
 - 6) Cy-C₂-10alkenyl,
 - 7) Cy-C₂-10alkynyl,

wherein alkyl, alkenyl, and alkynyl are optionally substituted with one to four substituents independently selected from R^a; and Cy is optionally substituted with one to four substituents independently selected from R^b;

- R² is
- 1) hydrogen,
 - 2) C₁-10alkyl,
 - 3) C₂-10alkenyl,
 - 4) C₂-10alkynyl,
 - 5) aryl,
 - 6) aryl-C₁-10alkyl,

- 7) heteroaryl,
- 8) heteroaryl-C₁₋₁₀alkyl,

wherein alkyl, alkenyl, and alkynyl are optionally substituted with one to four substituents independently selected from R^a; and aryl and
5 heteroaryl optionally substituted with one to four substituents independently selected from R^b;

- R³ is
- 1) hydrogen,
 - 2) C₁₋₁₀ alkyl,
 - 10 3) Cy, or
 - 4) Cy-C₁₋₁₀ alkyl,

wherein alkyl is optionally substituted with one to four substituents independently selected from R^a; and Cy is optionally substituted with one to four substituents independently selected from R^b;

- 15 R⁴ is
- 1) hydrogen,
 - 2) C₁₋₁₀alkyl,
 - 3) C₂₋₁₀alkenyl,
 - 4) C₂₋₁₀alkynyl,
 - 20 5) Cy,
 - 6) Cy-C₁₋₁₀alkyl,
 - 7) Cy-C₂₋₁₀alkenyl,
 - 8) Cy-C₂₋₁₀alkynyl,

wherein alkyl, alkenyl and alkynyl are optionally substituted with one to
25 four substituents selected from phenyl and R^x, and Cy is optionally substituted with one to four substituents independently selected from R^y;
or

R³, R⁴ and the atoms to which they are attached together form a mono-
or bicyclic ring containing 0-2 additional heteroatoms selected from N, O
30 and S;

- R⁵ is
- 1) hydrogen,
 - 2) C₁₋₁₀alkyl,

- 3) C₂₋₁₀alkenyl,
 4) C₂₋₁₀alkynyl,
 5) aryl,
 6) aryl-C₁₋₁₀alkyl,
 5 7) heteroaryl,
 8) heteroaryl-C₁₋₁₀alkyl,

wherein alkyl, alkenyl and alkynyl are optionally substituted with one to four substituents selected from R^x, and aryl and heteroaryl are optionally substituted with one to four substituents independently
 10 selected from R^y; or

R⁴, R⁵ and the carbon to which they are attached form a 3-7 membered mono- or bicyclic ring containing 0-2 heteroatoms selected from N, O and S;
 15

R⁶, R⁷, and R⁸ are each independently selected from the group consisting of

- 1) a group selected from R^d, and
 2) a group selected from R^x; or
 20 two of R⁶, R⁷, and R⁸ and the atom to which both are attached, or two of R⁶, R⁷, and R⁸ and the two adjacent atoms to which they are attached, together form a 5-7 membered saturated or unsaturated monocyclic ring containing zero to three heteroatoms selected from N, O or S,

- 25 R^a is 1) Cy, or
 2) a group selected from R^x;

wherein Cy is optionally substituted with one to four substituents independently selected from R^c;

- 30 R^b is 1) a group selected from R^a,
 2) C₁₋₁₀ alkyl,
 3) C₂₋₁₀ alkenyl,
 4) C₂₋₁₀ alkynyl,

- 5) aryl C₁₋₁₀alkyl,
- 6) heteroaryl C₁₋₁₀ alkyl,

wherein alkyl, alkenyl, alkynyl, aryl, heteroaryl are optionally substituted with a group independently selected from R^c;

5

- R^c is
- 1) halogen,
 - 2) NO₂,
 - 3) C(O)OR^f,
 - 4) C₁₋₄alkyl,
 - 10 5) C₁₋₄alkoxy,
 - 6) aryl,
 - 7) aryl C₁₋₄alkyl,
 - 8) aryloxy,
 - 9) heteroaryl,
 - 15 10) NR^fR^g,
 - 11) NR^fC(O)R^g,
 - 12) NR^fC(O)NR^fR^g, or
 - 13) CN;

- 20 R^d and R^e are independently selected from hydrogen, C₁₋₁₀alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀alkynyl, Cy and Cy C₁₋₁₀alkyl, wherein alkyl, alkenyl, alkynyl and Cy is optionally substituted with one to four substituents independently selected from R^c; or

- 25 R^d and R^e together with the atoms to which they are attached form a heterocyclic ring of 5 to 7 members containing 0-2 additional heteroatoms independently selected from oxygen, sulfur and nitrogen;

R^f and R^g are independently selected from hydrogen, C₁₋₁₀alkyl, Cy and Cy-C₁₋₁₀alkyl wherein Cy is optionally substituted with C₁₋₁₀alkyl; or

- 30 R^f and R^g together with the carbon to which they are attached form a ring of 5 to 7 members containing 0-2 heteroatoms independently selected from oxygen, sulfur and nitrogen;

- R^h is
- 1) hydrogen,
 - 2) C_{1-10} alkyl,
 - 3) C_{2-10} alkenyl,
 - 4) C_{2-10} alkynyl,
 - 5) cyano,
 - 6) aryl,
 - 7) aryl C_{1-10} alkyl,
 - 8) heteroaryl,
 - 9) heteroaryl C_{1-10} alkyl, or
 - 10) $-SO_2R^i$;

wherein alkyl, alkenyl, and alkynyl are optionally substituted with one to four substituents independently selected from R^a ; and aryl and heteroaryl are each optionally substituted with one to four substituents independently selected from R^b ;

- R^i
- 1) C_{1-10} alkyl,
 - 2) C_{2-10} alkenyl,
 - 3) C_{2-10} alkynyl, or
 - 4) aryl;

wherein alkyl, alkenyl, alkynyl and aryl are each optionally substituted with one to four substituents independently selected from R^c ;

- R^x is
- 1) $-OR^d$,
 - 2) $-NO_2$,
 - 3) halogen
 - 4) $-S(O)_mR^d$,
 - 5) $-SR^d$,
 - 6) $-S(O)_2OR^d$,
 - 7) $-S(O)_mNR^dR^e$,
 - 8) $-NR^dR^e$,
 - 9) $-O(CR^fR^g)_nNR^dR^e$,
 - 10) $-C(O)R^d$,
 - 11) $-CO_2R^d$,

- 12) $-\text{CO}_2(\text{CR}^f\text{R}^g)_n\text{CONR}^d\text{R}^e$,
 13) $-\text{OC}(\text{O})\text{R}^d$,
 14) $-\text{CN}$,
 15) $-\text{C}(\text{O})\text{NR}^d\text{R}^e$,
 5 16) $-\text{NR}^d\text{C}(\text{O})\text{R}^e$,
 17) $-\text{OC}(\text{O})\text{NR}^d\text{R}^e$,
 18) $-\text{NR}^d\text{C}(\text{O})\text{OR}^e$,
 19) $-\text{NR}^d\text{C}(\text{O})\text{NR}^d\text{R}^e$,
 20) $-\text{CR}^d(\text{N}-\text{OR}^e)$,
 10 21) $-\text{CF}_3$,
 22) oxo,
 23) $\text{NR}^d\text{C}(\text{O})\text{NR}^d\text{SO}_2\text{R}^i$,
 24) $\text{NR}^d\text{S}(\text{O})_m\text{R}^e$,
 25) $-\text{OS}(\text{O})_2\text{OR}^d$, or
 15 26) $-\text{OP}(\text{O})(\text{OR}^d)_2$;

- R^j is
- 1) a group selected from R^x ,
 2) C_{1-10} alkyl,
 3) C_{2-10} alkenyl,
 20 4) C_{2-10} alkynyl,
 5) aryl C_{1-10} alkyl,
 6) heteroaryl C_{1-10} alkyl,
 7) cycloalkyl,
 8) heterocyclyl;

25 wherein alkyl, alkenyl, alkynyl and aryl are each optionally substituted with one to four substituents independently selected from R^x ;

Cy is cycloalkyl, heterocyclyl, aryl, or heteroaryl;

30 m is an integer from 1 to 2;

n is an integer from 1 to 10;

- X is
- 1) -C(O)OR^d,
 - 2) -P(O)(OR^d)(OR^e)
 - 3) -P(O)(R^d)(OR^e)
 - 4) -S(O)_mOR^d,
 - 5) -C(O)NR^dR^h, or
 - 6) -5-tetrazolyl;

- Y is
- 1) -C(O)-,
 - 2) -O-C(O)-,
 - 3) -NR^e-C(O)-,
 - 4) -S(O)₂-,
 - 5) -P(O)(OR⁴) or
 - 6) C(O)C(O);

Z and A are independently selected from -C- and -C-C-;

B is selected from the group consisting of

- 1) a bond,
- 2) -C-
- 3) -C-C-,
- 3) -C=C-,
- 4) a heteroatom selected from the group consisting of nitrogen, oxygen, and sulfur; and
- 5) -S(O)_m-.

2. A method of Claim 1 wherein in compounds of

Formula I,

Y is S(O)₂;

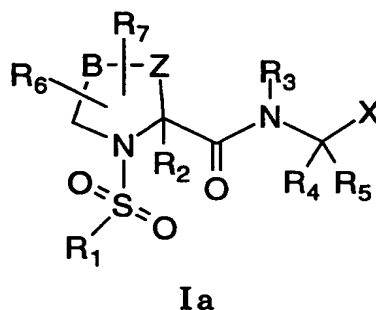
- R¹ is
- (1) C₁₋₁₀alkyl,
 - (2) Cy, or
 - (3) Cy-C₁₋₁₀ alkyl;

wherein alkyl is optionally substituted with one to two substituents independently selected from R^a, and Cy is optionally substituted with one to four substituents independently selected from R^b.

5 3. A method of Claim 1 wherein said cell adhesion is mediated by VLA-4.

 4. A method of Claim 1 wherein said disease is selected from asthma, allergic rhinitis, multiple sclerosis, atherosclerosis,
10 inflammatory bowel disease and inflammation.

 5, A compound having the formula Ia:



15

or a pharmaceutically acceptable salt thereof, wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, X, B, and Z are as defined in Claim 1 with the proviso that R⁶/R⁷ is not oxo when attached to the carbon between N and B, and with the further proviso that when B and Z are each C, R², R³, R⁶, and R⁷ are each H, then R¹ is other than phenyl, 4-methylphenyl and 5-(NR^dRe)naphthyl.

20

 6. A compound of Claim 5 wherein Z is C.

25

 7. A compound of Claim 5 wherein B is C, C=C, C-C or S.

8. A compound of Claim 5 wherein X is C(O)OR^d.

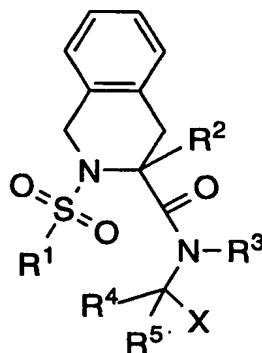
9. A compound of Claim 5 wherein R¹ is C₁-10alkyl, Cy or Cy-C₁-10alkyl wherein alkyl is optionally substituted with one to two
5 substituents independently selected from R^a, and Cy is optionally substituted with one to four substituents independently selected from R^b.

10. A compound of Claim 5 wherein R¹ is aryl optionally substituted with one to four substituents selected from R^b.

11. A compound of Claim 5 wherein R⁵ is H and R⁴ is C₁-10 alkyl or Cy-C₁-10alkyl, wherein alkyl is optionally substituted with one to four substituents selected from phenyl and R^x, and Cy is optionally substituted with one to four substituents independently selected from R^y;
15 or R⁴, R⁵ and the carbon to which they are attached together form a 3-7 membered mono- or bicyclic carbon only ring.

12. A compound of Claim 11 wherein R⁴ is phenyl-C₁-3 alkyl, wherein phenyl is optionally substituted with one or two groups
20 selected from R^y.

13. A compound of Claim 5 having the formula Ib:



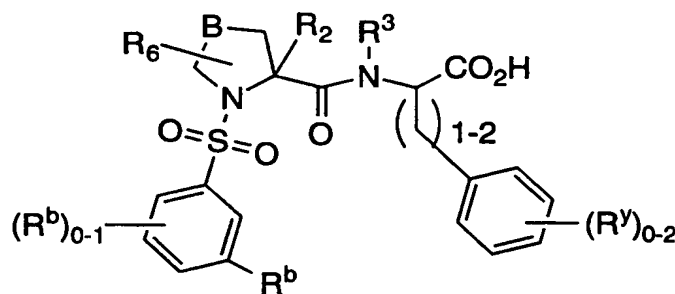
Ib

wherein R² is H or C₁₋₆ alkyl, and R¹, R², R³, R⁴ and R⁵ and X are as defined in Claim 5.

- 5 14. A compound of Claim 13 wherein X is CO₂H; R¹ is aryl optionally substituted with one to four substituents selected from R^b; R² is H; R³ H or C₁₋₃ alkyl; R⁴ is phenyl-C₁₋₃alkyl, wherein phenyl is optionally substituted with one or two groups selected from R^y; and R⁵ is H.

10

15. A compound of Claim 5 having the formula Ic:



15

Ic

wherein R² is H or C₁₋₃ alkyl; R⁶ is H, C₁₋₆ alkyl, aryl, OR^d, SR^d, NR^dRe, or NR^dC(O)Re; B is S, C=C, C or C-C; R³ is H or C₁₋₆alkyl, R^b and R^y are as defined in Claim 5.

20

16. A compound of Claim 15 wherein B is C and R^b is halogen, C₁₋₁₀alkoxy, cyano, or trifluoromethyl.

17. A compound selected from the group consisting of:
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-leucine;

N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-arginine;
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-glutamic acid;
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-glycine;
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-(1-naphthyl)alanine;
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)- α -t-butylglycine;
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-3-(2-thienyl)alanine;
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-cyclohexylalanine;
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-3-(2-naphthyl)alanine;
N-(3,3-diphenylpropanoyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;
N-(2,4-dinitrobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-3,3-diphenylalanine;
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid;
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-proline;
N-dansyl-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;
N-(2-naphthalenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;
N-(4-methoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;

N-(4-phenylbenzoyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;
N-(3,4-dimethylbenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-cysteine;
N-(4-t-butylbenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;
N-(2,5-dichlorobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;
N-(2-mesitylenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;
N-(p-toluenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;
N-(4-chlorobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;
N-(N'-acetylsulfanilyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;
N-(4-fluorobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;
N-(1-naphthalenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;
N-(benzylsulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;
N-(4-nitrobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-phenylalanine;
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-glutamine;
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-(4-nitrophenyl)alanine;
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-asparagine;

N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-methionine;
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-homophenylalanine;
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(D)-norleucine;
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-(4-fluorophenyl)alanine;
N-(3-toluenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;
N-(4-trifluoromethylbenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;
N-(4-n-propylbenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;
N-(4-isopropylbenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;
N-(2,6-dichlorobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;
N-(4-ethylbenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;
N-(2,4-difluorobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;
N-(2-cyanobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;
N-(4-tert-amylbenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;
N-(4-chloro-3-nitrobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;
N-(3-cyanobenzoyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;
N-(3,5-dichlorobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;

N-(3,4-dichlorobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl(L)-norleucine;
N-(2-trifluoromethylbenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl(L)-norleucine;
N-(2,3-dichlorobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl(L)-norleucine;
N-(2,4-dichlorobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl(L)-norleucine;
N-(2,5-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl(L)-norleucine;
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl(L)-serine;
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl(L)-isoleucine;
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl(L)-tryptophan;
N-(2,1,3-benzothiadiazole-4-sulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl(L)-tryptophan;
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl(L)-3-(3-pyridyl)alanine;
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl(L)-3-(2-naphthyl)alanine, ethyl ester;
N-acetyl-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl(L)-norleucine;
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(R)-carbonyl(D)-norleucine;
N-propionyl(L)-prolyl-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl(L)-norleucine;
N-(4-cyanobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl(L)-norleucine;
N-(benzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl(L)-norleucine;

N-(3-nitrobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-
carbonyl-(L)-norleucine;
N-(3-trifluoromethylbenzenesulfonyl)-1,2,3,4-
tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;
N-(2-thienylsulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-
(L)-norleucine;
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-
3(S)-carbonyl-(L)-N-methylleucine;
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-
3(S)-carbonyl-(L)-citrulline;
N-(4-iodobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-
carbonyl-(L)-norleucine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-(3-iodo)tyrosine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-3-(3-pyridyl)alanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-phenylalanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-glutamic acid;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-arginine;
N-(N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl)-1-amino-
cyclopentane-1-carboxylic acid;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-3-(3,4-
dichlorophenyl)alanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-3-(2-
naphthyl)alanine, ethyl ester;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-3-(4-
bromophenyl)alanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-3-(4-
nitrophenyl)alanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-3-(4-
thiazolyl)alanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-3-(2-
chlorophenyl)alanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-3-(4-
chlorophenyl)alanine;

N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-3-(4-cyanophenyl)alanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-tyrosine, O-sulfate;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-3,5-diiodotyrosine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-tyrosine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-aspartic acid;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-tryptophan;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-methionine;
N-(3,4-dimethoxybenzenesulfonyl)-(L)-prolyl-(L)-norleucine;
N-(3,5-di(trifluoromethyl)benzenesulfonyl)-(L)-prolyl-(L)-3-(2-naphthyl)alanine;
N-(3,4-dimethoxybenzenesulfonyl)-(L)-thiaprolyl-(L)-3-(2-naphthyl)alanine;
N-(3,4-dimethoxybenzenesulfonyl)-(L)-thiaprolyl-(L)-norleucine;
N-[4-(N'-2-toluy lureido)phenylacetyl]-(L)-thiaprolyl-(L)-3-(2-naphthyl)alanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-thiaprolyl-(L)-3-(2-naphthyl)alanine;
N-(3,4-dimethoxybenzenesulfonyl)-(L)-pipecolyl-(L)-norleucine;
N-(3,4-dimethoxybenzenesulfonyl)-(L)-pipecolyl-(L)-norleucine, ethyl ester;
N-(3,5-dichlorobenzenesulfonyl)-(L)-pipecolyl-(L)-homophenylalanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-pipecolyl-(L)-(3-iodo)tyrosine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-pipecolyl-(L)-3-(2-naphthyl)alanine;
N-[4-(N'-2-toluy lureido)phenylacetyl]-(L)-pipecolyl-(L)-3-(2-naphthyl)alanine;
N-[3,5-di(trifluoromethyl)benzenesulfonyl]-(L)-pipecolyl-(L)-3-(2-naphthyl)alanine;
N-(3,4-dimethoxybenzenesulfonyl)-(L)-pipecolyl-(L)-3-(2-naphthyl)alanine, ethyl ester;

N-(3,4-dimethoxybenzenesulfonyl)-(L)-octahydroisoquinoline-3-carbonyl-(L)-norleucine;
N-(3,4-dimethoxybenzenesulfonyl)-azetidine-2-carbonyl-(L)-norleucine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-4(S)-hydroxypropyl-(L)-3-(2-naphthyl)alanine;
N-(3,4-dimethoxybenzenesulfonyl)-(L)-4(S)-hydroxypropyl-(L)-norleucine;
N-(3,4-dimethoxybenzenesulfonyl)-(L)-3,4-dehydropropyl-(L)-norleucine;
N-(3-bis(N,N-benzenesulfonyl)aminobenzenesulfonyl)-(L)-propyl-(L)-norleucine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-propyl-(L)-3-(4-pyridyl)alanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-4(R)-aminopropyl-(L)-3-(2-naphthyl)alanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-3,4-dehydropropyl-(L)-4-fluorophenylalanine;
N-(3-chlorobenzenesulfonyl)-(L)-propyl-(L)-4-fluorophenylalanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-4(R)-hydroxypropyl-(L)-4-fluorophenylalanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-thiaprolyl-(L)-tyrosine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-thiaprolyl-(L)-3-iodotyrosine;
N-(3-fluorobenzenesulfonyl)-(L)-thiaprolyl-(L)-3-(2-naphthyl)alanine;
N-(3-fluorobenzenesulfonyl)-(L)-pipecolyl-(L)-3-(2-naphthyl)alanine;
N-(3-fluorobenzenesulfonyl)-(L)-thiaprolyl-(L)-4-fluorophenylalanine;
N-(3-fluorobenzenesulfonyl)-(L)-propyl-(L)-4-fluorophenylalanine;
N-(3-chlorobenzenesulfonyl)-(L)-3,4-dehydropropyl-(L)-4-fluorophenylalanine;
N-(3-fluorobenzenesulfonyl)-(L)-4(R)-hydroxypropyl-(L)-4-fluorophenylalanine;

N-(3-chlorobenzenesulfonyl)-(L)-4(R)-hydroxypropyl-(L)-4-fluorophenylalanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-pipecolyl-(L)-4-fluorophenylalanine;
N-(3-fluorobenzenesulfonyl)-(L)-3,4-dehydropropyl-(L)-tyrosine;
N-(4,5-dichloro-2-thiophenesulfonyl)-(L)-propyl-(L)-tyrosine;
N-(3-fluorobenzenesulfonyl)-(L)-4(R)-hydroxypropyl-(L)-tyrosine;
N-(3-chlorobenzenesulfonyl)-(L)-4(R)-hydroxypropyl-(L)-tyrosine;
N-(3-fluorobenzenesulfonyl)-(L)-pipecolyl-(L)-4-fluorophenylalanine;
N-(3-fluorobenzenesulfonyl)-(L)-4(R)-hydroxypropyl-(L)-tyrosine, O-tert-butyl ether;
N-(3-chlorobenzenesulfonyl)-(L)-4(R)-hydroxypropyl-(L)-tyrosine, O-tert-butyl ether;
N-(4,5-dichloro-2-thiophenesulfonyl)-(L)-3,4-dehydropropyl-(L)-tyrosine
N-(3,5-dichlorobenzenesulfonyl)-(L)-3(S)-methyl-propyl-(L)-4-fluorophenylalanine;
N-(4,5-dichloro-2-thiophenesulfonyl)-(L)-3,4-dehydropropyl-(L)-tyrosine;
N-(3-fluorobenzenesulfonyl)-(L)-3,4-dehydropropyl-(L)-tyrosine, O-tert-butyl ether;
N-(3-chlorobenzenesulfonyl)-(L)-3,4-dehydropropyl-(L)-tyrosine, O-tert-butyl ether;
N-(3-chlorobenzenesulfonyl)-(L)-2(S)-methyl-propyl-(L)-4-fluorophenylalanine;
N-(3-chlorobenzenesulfonyl)-(L)-2(S)-methyl-propyl-(L)-tyrosine;
N-(3-chlorobenzenesulfonyl)-(L)-2(S)-methyl-propyl-(L)-tyrosine, O-tert-butyl ether;
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-propyl-(L)-tyrosine;
N-(3-fluorobenzenesulfonyl)-(L)-propyl-(L)-3-iodotyrosine;
N-(3-chlorobenzenesulfonyl)-(L)-propyl-(L)-3-iodotyrosine;

N-(3-fluorobenzenesulfonyl)-(L)-prolyl-(L)-3-phenylalanine;
N-(3-chlorobenzenesulfonyl)-(L)-prolyl-(L)-phenylalanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-phenylalanine;
N-(3-fluorobenzenesulfonyl)-(L)-4(R)-hydroxyprolyl-(L)-phenylalanine;
N-(3-chlorobenzenesulfonyl)-(L)-4(R)-hydroxyprolyl-(L)-phenylalanine;
N-(4,5-dichloro-2-thiophenesulfonyl)-(L)-3,4-dehydroprolyl-(L)-3-(4-pyridyl)alanine;
N-(4,5-dichloro-2-thiophenesulfonyl)-(L)-thiaprolyl-(L)-3-(4-pyridyl)alanine;
N-(4,5-dichloro-2-thiophenesulfonyl)-(L)-3,4-dehydroprolyl-(L)-4-fluorophenylalanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-4(R)-hydroxyprolyl-(L)-phenylalanine;
N-(3-trifluoromethylbenzenesulfonyl)-(L)-prolyl-(L)-4-fluorophenylalanine;
N-(3-trifluoromethylbenzenesulfonyl)-(L)-thiaprolyl-(L)-4-fluorophenylalanine;
N-(3-fluorobenzenesulfonyl)-(L)-3,4-dehydroprolyl-(L)-4-fluorophenylalanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-tyrosine, O-phosphoric acid;
N-(3-chlorobenzenesulfonyl)-(L)-4(R)-aminoprolyl-(L)-tyrosine;
N-(4,5-dichloro-2-thiophenesulfonyl)-(L)-thiaprolyl-(L)-tyrosine;
N-(N₁-methyl-4-imidazolesulfonyl)-(L)-prolyl-(L)-4-fluorophenylalanine;
N-(3,5-dichlorobenzenesulfonyl)-(D)-prolyl-(D)-4-fluorophenylalanine;
N-(4,5-dichloro-2-thiophenesulfonyl)-(L)-4(R)-aminoprolyl-(L)-3-(4-pyridyl)alanine;
N-(5-(5-trifluoromethyl-2-pyridylsulfonyl)-2-thiophenesulfonyl)-(L)-prolyl-(L)-4-fluorophenylalanine;

N-(5-(N-(4-chlorobenzoyl)aminomethyl))-2-thiophenesulfonyl)-(L)-prolyl-(L)-4-fluorophenylalanine;
N-(5-(3-(1-methyl-5-trifluoromethyl-pyrazoyl))-2-thiophenesulfonyl)-(L)-prolyl-(L)-4-fluorophenylalanine;
N-(3-fluorobenzenesulfonyl)-2(S)-methylprolyl-(L)-O-tert-butyl-tyrosine;
N-(3-fluorobenzenesulfonyl)-(L)-4(R)-aminoprolyl-(L)-4-fluorophenylalanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-4(R)-aminoprolyl-(L)-4-fluorophenylalanine;
N-(3-chlorobenzenesulfonyl)-(L)-4(R)-aminoprolyl-(L)-4-fluorophenylalanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-4(S)-aminoprolyl-(L)-4-fluorophenylalanine;
N-(3-chlorobenzenesulfonyl)-(L)-thiaprolyl-(L)-4-fluorophenylalanine;
N-(4-bromo-5-chloro-2-thiophenesulfonyl)-(L)-prolyl-(L)-4-fluorophenylalanine;
N-(4,5-dichloro-2-thiophenesulfonyl)-(L)-prolyl-(L)-4-fluorophenylalanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-thiaprolyl-(L)-3,5-diiodotyrosine;
N-(5-benzoylaminomethyl-2-thiophenesulfonyl)-(L)-prolyl-(L)-4-fluorophenylalanine;
N-(3-chlorobenzenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine;
N-(5-benzenesulfonyl-2-thiophenesulfonyl)-(L)-prolyl-(L)-4-fluorophenylalanine;
N-(3-bromo-5-chloro-2-thiophenesulfonyl)-(L)-prolyl-(L)-4-fluorophenylalanine;
N-(3-chlorobenzenesulfonyl)-(L)-3,4-dehydroprolyl-(L)-tyrosine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-homophenylalanine;

N-(4-benzenesulfonyl-2-thiophenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine;
N-(5-benzoylaminomethyl-2-thiophenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine;
N-(trans-2-phenyl-ethylene-sulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine;
N-(5-benzenesulfonyl-2-thiophenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine;
N-(3-fluorobenzenesulfonyl)-(L)-thiaprolyl-(L)-O-tert-butyl-tyrosine;
N-(benzylsulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-cysteine, amide;
N-(1-methyl-4-imidazolylsulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine;
N-(4-(N-(4-dimethylaminophenyl)diazo)-benzenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine;
N-(5-(4-trifluoromethylbenzenesulfonyl)-2-thiophenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine;
N-(3-bromobenzenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine;
N-(4-methylsulfonyl-benzenesulfonyl)-(L)-prolyl-(L)-4-fluorophenylalanine;
N-(4-methoxybenzenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine;
N-(4,5-dichloro-2-thiophenesulfonyl)-(L)-prolyl-(L)-3-fluorophenylalanine;
N-(5-chloro-2-thiophenesulfonyl)-(L)-prolyl-(L)-4-fluorophenylalanine;
N-(3-chlorobenzenesulfonyl)-(L)-thiaprolyl-(L)-tyrosine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methylprolyl-(L)-O-tert-butyl-tyrosine;
N-(1(R)-(+)-10-camphorsulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine;
N-(1(S)-(+)-10-camphorsulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine;

N-(3,4-methylenedioxy-phenylacetyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine;
N-(3-chlorobenzenesulfonyl)-(L)-4(R)-hydroxyprolyl-(L)-tyrosine-O-sulfate;
N-(3-chlorobenzenesulfonyl)-(L)-thiaprolyl-(L)-tyrosine-O-sulfate;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-cysteine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-N-methyl-isoleucine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-4(R)-aminoprolyl-(L)-O-tert-butyl-tyrosine;
N-(3-chlorobenzenesulfonyl)-(L)-4(R)-aminoprolyl-(L)-O-tert-butyl-tyrosine;
N-(3-cyanobenzenesulfonyl)-(L)-prolyl-(L)-tyrosine;
N-benzenesulfonyl-(L)-prolyl-(L)-O-tert-butyl-tyrosine;
N-(4-methylsulfonylbenzenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine;
N-(4,5-dichloro-2-thiophenesulfonyl)-(L)-4(R)-aminoprolyl-(L)-O-tert-butyl-tyrosine;
N-(4,5-dichloro-2-thiophenesulfonyl)-(L)-4(R)-aminoprolyl-(L)-4-fluorophenylalanine;
N-(9-fluorenylmethyloxycarbonyl)-(L)-prolyl-(L)-phenylalanine;
N-(benzenesulfonyl)-(L)-prolyl-(L)-phenylalanine;
N-(n-octyl-1-sulfonyl)-(L)-prolyl-(L)-phenylalanine;
N-(3-fluorobenzenesulfonyl)-(L)-5(R)-phenyl-prolyl-(L)-4-fluorophenylalanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-3(R)-phenyl-prolyl-(L)-4-iodophenylalanine;
N-(3,5-dichlorobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-1-carbonyl-(L)-4-fluorophenylalanine;
N-(3,5-dichlorobenzenesulfonyl)-1,3-dihydro isoindolyl-1-carbonyl-(L)-4-fluorophenylalanine;
N-(4-(fluorescien-4-carbonylamino)benzene sulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine;

N-(3-ethoxycarbonyl-benzenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine;
N-(4-iodobenzenesulfonyl)-(L)-prolyl-(L)-4-benzoyl-phenylalanine;
N-(3-(4-benzophenonyl-carbonylamino)-benzenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine;
N-(3-(6-(biotinylamino)-n-hexanoyl)-aminobenzenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine;
N-(3,5-dichlorobenzenesulfonyl)-[3.1.0]-3-azabicyclohexane-2-carbonyl-(L)-4-fluorophenylalanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-3-(2-naphthyl)alanine;
N-[4-(N'-2-toluy lureido)phenylacetyl-(L)-prolyl-(L)-norleucine;
N-(3,4-dimethoxybenzoyl)-(L)-prolyl-(L)-norleucine;
N-(3,4-dimethoxybenzenesulfonyl)-(L)-pipecolyl-(L)-tryptophan;
N-(4-nitrobenzenesulfonyl)-(L)-prolyl-(L)-norleucine;
N-[3,5-di(trifluoromethyl)benzenesulfonyl)-(L)-prolyl-(L)-norleucine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-norleucine;
N-(3-trifluoromethylbenzenesulfonyl)-(L)-prolyl-(L)-norleucine;
N-[4-(benzoylamino)benzenesulfonyl)-(L)-prolyl-(L)-norleucine;
N-(4-methoxy-3,5-dinitrobenzenesulfonyl)-(L)-prolyl-(L)-norleucine;
N-(3-chlorobenzenesulfonyl)-(L)-prolyl-(L)-norleucine;
N-(3-trifluoromethylbenzenesulfonyl)-(L)-prolyl-(L)-3-(2-naphthyl)alanine;
N-(3-nitrobenzenesulfonyl)-(L)-prolyl-(L)-norleucine;
N-(3-cyanobenzenesulfonyl)-(L)-prolyl-(L)-norleucine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-tryptophan;
N-(3-methylbenzenesulfonyl)-(L)-prolyl-(L)-norleucine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-3(S)-methyl-prolyl-(L)-3-(2-naphthyl)alanine;
N-(3-chlorobenzenesulfonyl)-(L)-prolyl-(L)-3-(2-naphthyl)alanine;
N-(3-fluorobenzenesulfonyl)-(L)-prolyl-(L)-3-(2-naphthyl)alanine;
N-phenylacetyl-(L)-prolyl-(L)-3-(2-naphthyl)alanine;

N-(3-phenylpropionyl)-(L)-prolyl-(L)-3-(2-naphthyl)alanine;
N-(phenylaminocarbonyl)-(L)-prolyl-(L)-3-(2-naphthyl)alanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-2-methyl-prolyl-(L)-3-(2-naphthyl)-alanine;
N-(benzenesulfonyl)-(L)-prolyl-(L)-3-(2-naphthyl)alanine;
N-(4-N'-phenylureidobenzenesulfonyl)-(L)-prolyl-(L)-3-(2-naphthyl)alanine;
N-(3-fluorobenzenesulfonyl)-(L)-5,5-dimethyl-prolyl-(L)-3-(2-naphthyl)alanine;
N-(4-N'-(2-toluy)ureidobenzenesulfonyl)-(L)-prolyl-(L)-3-(2-naphthyl)alanine;
N-(3-fluorobenzenesulfonyl)-(L)-prolyl-(L)-4-iodophenylalanine;
N-(4-N'-benzylureidobenzenesulfonyl)-(L)-prolyl-(L)-3-(2-naphthyl)alanine;
N-(phenyloxalyl)-(L)-prolyl-(L)-3-(2-naphthyl)alanine;
N-(benzylaminocarbonyl)-(L)-prolyl-(L)-3-(2-naphthyl)alanine;
N-(3-fluorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-fluorophenylalanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-fluorophenylalanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-phenylalaninamide-N-methylsulfonamide;
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-iodophenylalanine;
N-(3-fluorobenzenesulfonyl)-(L)-prolyl-(L)-phenylalanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-5-methylprolyl-(L)-4-fluorophenylalanine;
N-(3,5-dichlorobenzenesulfonyl)-3-phenylazetidiny carbonyl-(L)-4-fluorophenylalanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-allylprolyl-(L)-4-fluorophenylalanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-phenylalanine;

N-(3-trifluoromethylbenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-nitro-phenylalanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-3(R)-methyl-prolyl-(L)-4-fluorophenylalanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-cyanophenylalanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(aminocarbonyl)-phenylalanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-3(R)-methyl-prolyl-(L)-4-(N-t-butoxycarbonylaminomethyl)-phenylalanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-3(R)-methyl-prolyl-(L)-4-(aminomethyl)-phenylalanine;
N-(3-trifluoromethylphenylsulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-acetaminophenylalanine;
N-(3-trifluoromethylphenylsulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(N'-(2-toluy)ureido)phenylalanine;
N-(3-trifluoromethylphenylsulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(N'-(4'-fluorophenylsulfonyl)ureido)phenylalanine;
N-(3-trifluoromethylphenylsulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(ethoxycarbonyl)aminophenylalanine;
N-(3-trifluoromethylphenylsulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(4'-(N'-(2-toluy)ureido)phenylacetyl)aminophenylalanine;
N-(3-trifluoromethylphenylsulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(4'-fluorophenylsulfonyl)aminophenylalanine;
N-(3-trifluoromethylphenylsulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(phenylacetyl)aminophenylalanine;
N-(3-trifluoromethylphenylsulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(4'-fluorobenzoyl)aminophenylalanine;
N-(3-trifluoromethylphenylsulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(isobutyloxycarbonyl)aminophenylalanine;
N-(3-trifluoromethylphenylsulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-methylsulfonylaminophenylalanine;

N-(3-trifluoromethylphenylsulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(N'-(4-fluorophenyl)ureido)phenylalanine;
N-(3-trifluoromethylbenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(N-(1,1-dioxo-1,2-isothiazolidinyl)-phenylalanine;
N-(3-trifluoromethylphenylsulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(N'-(4-(2-oxo-1-pyrrolidinyl)-phenylalanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(4'-fluorobenzoyl)phenylalanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4'-(2-methoxybenzoyl)phenylalanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(4'-fluorobenzoyl)phenylalanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(4-fluorobenzyl)phenyl alanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(2-methoxybenzyl)phenylalanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(2-nitrophenoxy)-phenylalanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(4-nitrophenoxy)-phenylalanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(2-nitrophenoxy)-phenylalanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(2-aminophenoxy)-phenylalanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(2-acetylaminophenoxy)-phenylalanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(4-acetylaminophenoxy)-phenylalanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methylprolyl-(L)-4-(2-acetylaminophenoxy)-phenylalanine;
N-(3,5-dichlorobenzenesulfonyl)-2-(S)-methyl-(L)-prolyl-4-(2-cyanophenoxy)-phenylalanine;

N-(3,5-dichlorobenzenesulfonyl)-2-(S)-methyl-(L)-prolyl-4-(4-cyanophenoxy)-phenylalanine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-methyl-tyrosine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-benzyl-tyrosine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-n-butyl-tyrosine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-cyanomethyl-tyrosine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-(2-methoxyethyl)-tyrosine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-(2-ethoxyethyl)-tyrosine;
N-(benzenesulfonyl)-(L)-prolyl-(L)-O-(2-methoxyethyl)-tyrosine;
N-(benzenesulfonyl)-(L)-prolyl-(L)-O-(2-ethoxyethyl)-tyrosine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-(1-pyrrolidinylcarbonyl)-tyrosine;
N-(benzenesulfonyl)-(L)-prolyl-(L)-O-(1-pyrrolidinylcarbonyl)-tyrosine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-(tert-butyl acetate)-tyrosine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-(4-morpholinylcarbonyl)-tyrosine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-(1-(2-propanonyl)-tyrosine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-O-(1-pyrrolidinylcarbonyl)-tyrosine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-O-(tert-butyl acetate)-tyrosine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-O-(2-ethoxyethyl)-tyrosine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-(acetic acid)-tyrosine, methyl ester;

N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-(acetic acid)-tyrosine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-O-(1-(2-propanonyl)-tyrosine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-O-(1-pyrrolidinylcarbonyl)-tyrosine, methyl ester;
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-O-(4-morpholinyl-carbonyl)-tyrosine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-(2-pyrrolylcarbonyl)-tyrosine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-O-(N-phenyl-N-methylaminocarbonyl)-tyrosine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-O-(N,N-diethyl-aminocarbonyl)-tyrosine;
N-(3-chlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-O-(4-morpholinyl-carbonyl)-tyrosine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-O-(N,N-diisopropyl-aminocarbonyl)-tyrosine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-(benzoyl)-tyrosine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-(cyclopentanoyl)-tyrosine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-(5-tetrazolyl)methyl-tyrosine;
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-N^ε-benzyl-histidine;
N-benzenesulfonyl-(L)-prolyl-2-amino-2-norbornanecarboxylic acid;
N-benzenesulfonyl-(L)-prolyl-3(R)-methyl-phenylalanine;
N-benzenesulfonyl-(L)-prolyl-(L)-2,3-methano-phenylalanine;
N-benzenesulfonyl-(L)-prolyl-(D)-2,3-methano-phenylalanine; and
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(5-((1H,3H)-1,3-dimethylpyrimidine-2,4-dione))-phenylalanine.

18. A method for the treatment of diseases, disorders, conditions or symptoms mediated by cell adhesion in a mammal which comprises administering to said mammal an effective amount of a compound of Claim 5.

5

19. A method for the treatment of asthma, allergic rhinitis, multiple sclerosis, atherosclerosis, inflammatory bowel disease or inflammation in a mammal which comprises administering to said mammal an effective amount of a compound of Claim 5.

10

20. A pharmaceutical composition which comprises a compound of Claim 5 and a pharmaceutically acceptable carrier thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/10940

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,424,329 A (BOSCHELLI et al.) 13 June 1995, see entire document.	1-20
A	BOSCHELLI et al. Inhibition of E-Selectin-, ICAM-1, and VCAM-1-Mediated Cell Adhesion by Benzo[b]thiophene-, Benzofuran-, Indole-, and Naphthalene-2-Carboxamides: Identification of PD 144795 as an Antiinflammatory Agent. J.Med.Chem. 1995. Vol. 38. pages 4597-46-14, especially page 4599, column 2, Scheme 7, page 4601, column 2, Table 5 and page 4602, column 1, Table 6.	1-20
Y	EP 0618221 A2 (BRISTOL-MYERS SQUIBB CO.) 05 October 1994, page 103, line 55; page 104, lines 1-31.	1, 2

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

25 AUGUST 1998

Date of mailing of the international search report

Name and mailing address of the ISA/IJS
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer
JANE E. OSWECKI

Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

 International application No.
PCT/US98/10940

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,602,099 A (SCHILLER) 11 February 1997, abstract.	4
Y	US 5,229,381 A (DOHERTY et al) 20 July 1993, col. 63, lines 40-68; col. 64, lines 1-17 and 49-52.	1-4
Y	Chem. abstr., Vol.107, No.11, 14 September 1987 (Columbus, OH, USA), page 731, column 2, the abstract No. 97096z, VOIGHT et al., 'Synthesis of N-alpha-(tosylprolylglycyl)- and N-alpha-(tosylglycylprolyl)-4-amindinophenylalanine amides as inhibitors of thrombin.' Pharmazie 1986, 41(6), 378-81 (Ger), see entire abstract.	5
Y	Chem. abstr., Vol.105, No.25, 22 December 1986 (Columbus, OH, USA), page 866, column 1, the abstract No. 227343z, KURAUCHI et al. 'Dipeptide derivatives and antihypertensive drugs containing them.' Eur. Pat. Appl. EP 190,852, 13 August 1986, see entire abstract.	5
Y	WO 92/04369 A1 (DEPHA TEAM S.R.L.) 19 March 1992, page 19, lines 1-26; page 20, lines 1-30; page 21, lines 10-13.	1, 2, 4-12, 15, 19
Y	Chem. abstr., Vol.120, No.9, 28 February 1994 (Columbus, OH, USA), page 1248, column 2, the abstract No. 107719q, PELLICCARI et al. 'Brush-border-enzyme-mediated intestine-specific drug delivery. Amino acid prodrugs of 5-aminosalicylic acid.' J. Med. Chem. 1993, 36(26), 4201-7 (Eng), see entire document.	1,2,4
Y	Chem. abstr., Vol.117, No.13, 28 September 1992 (Columbus, OH, USA), page 108, column 1, the abstract No. 131564u, PELLICCIARI et al. 'preparation of 5-aminosalicylic acid derivatives for the therapy of chronic inflammatory bowel diseases.' PCT Int. Appl. WO 92/04,369, 19 March 1992, see entire document.	1,3,4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/10940

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6A(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☒ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/10940

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6):

A61K 31/395, 31/40, 31/41, 31/415, 31/425, 31/435, 31/44, 31/445, 31/47, 31/495, 31/535; C07D 205/02, 209/04, 209/14, 209/30, 217/12, 235/02, 233/64, 241/02, 257/04, 265/30, 275/02, 277/02, 277/08, 295/08, 295/26, 401/02, 401/12, 401/14, 413/02, 413/12, 413/14, 417/02, 417/12, 417/14, 487/04, 513/04; C07F 9/02

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

514/210, 231.5, 237.5, 237.8, 238.2, 255, 277, 307, 309, 323, 343, 369, 372, 381, 382, 393, 397, 398, 415, 419; 544/141, 158, 337, 406; 546/141, 146, 201, 262, 276.4; 548/182, 188, 189, 206, 213, 214, 251, 252, 254, 303.1, 338.1, 469, 470, 472, 492, 503, 950, 953

B. FIELDS SEARCHED

Minimum documentation searched

Classification System: U.S.

514/210, 231.5, 237.5, 237.8, 238.2, 255, 277, 307, 309, 323, 343, 369, 372, 381, 382, 393, 397, 398, 415, 419; 544/141, 158, 337, 406; 546/141, 146, 201, 262, 276.4; 548/182, 188, 189, 206, 213, 214, 251, 252, 254, 303.1, 338.1, 469, 470, 472, 492, 503, 950, 953

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

APS, CAS ONLINE, MEDLINE, BIOSIS

search terms: heterocycl?, sulfonamid?, sulphonamid?, carboxamid?, cell (L) adhesi?(L)inhibit?, metasta?, cancer?, oncol?

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid:

Group I, claims 5 and 17, drawn to compounds of formulae I, Ia, Ib and Ic having pyrrolidine as the only heterocyclic substituent.

Group II, claims 5 and 17, drawn to compounds of formulae I, Ia, Ib and Ic having tetrazole as a heterocyclic substituent.

Group III, claims 5 and 17, drawn to compounds of formulae I, Ia, Ib and Ic having morpholine as a heterocyclic substituent.

Group IV, claims 5 and 17, drawn to compounds of formulae I, Ia, Ib and Ic having thiazolidine or isothiazolidine.

Group V, claims 5 and 17, drawn to compounds of formulae I, Ia, Ib and Ic having biotin as a heterocyclic substituent.

Group VI, claims 5 and 17, drawn to compounds of formulae I, Ia, Ib and Ic having indole or isoindole as a heterocyclic substituent.

Group VII, claims 5 and 17, drawn to compounds of formulae I, Ia, Ib and Ic having pyrazine as a heterocyclic substituent.

Group VIII, claims 5 and 17, drawn to compounds of formulae I, Ia, Ib and Ic having imidazole as a heterocyclic substituent.

Group IX, claims 5 and 17, drawn to compounds of formulae I, Ia, Ib and Ic having pipercolate as a heterocyclic substituent.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/10940

Group X, claims 5 and 17, drawn to compounds of formulae I, Ia, Ib and Ic having pyridine as a heterocyclic substituent.

Group XI, claims 5 and 17, drawn to compounds of formulae I, Ia, Ib and Ic having azetidine as a heterocyclic substituent.

Group XII, claims 5 and 17, drawn to compounds of formulae I, Ia, Ib and Ic having isoquinoline as a heterocyclic substituent.

Group XIII, claims 5 and 17, drawn to exemplified compounds of formulae I, Ia, Ib and Ic which are not otherwise embraced by the groups provided *supra*.

Claims 1-4, 6-16 and 18-20 will be examined as commensurate in scope with the group elected.

The inventions listed as Groups I-XIII do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, no single special technical feature that makes a contribution over the prior art is shared by all the groups listed, i.e., each core moiety is different in structure and these core moieties are not known as equivalents in the art.

The structural moiety shared by all the inventions listed as Groups I-XIII, i.e., a nitrogen-containing heterocyclic group substituted by a further substituted carboxamide group, is known in the prior art and hence does not make a contribution over that art (see U.S. Pat. 4,098,904 to Szmuszkowicz).

10

PCTORGANISATION FÜR GEISTIGES EIGENTUM
Internationales BüroINTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE
INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

(51) Internationale Patentklassifikation ⁶ : C07D 213/81, A61K 31/495, C07D 271/06, 295/22, 295/20, 333/34, 215/36, 311/74, 333/38, 213/18, 261/10, 333/70, 317/68, 413/12		A1	(11) Internationale Veröffentlichungsnummer: WO 99/16751 (43) Internationales Veröffentlichungsdatum: 8. April 1999 (08.04.99)
(21) Internationales Aktenzeichen: PCT/EP98/05898 (22) Internationales Anmeldedatum: 16. September 1998 (16.09.98) (30) Prioritätsdaten: 197 43 435.5 1. Oktober 1997 (01.10.97) DE (71) Anmelder (für alle Bestimmungsstaaten ausser US): MERCK PATENT GMBH [DE/DE]; D-64271 Darmstadt (DE). (72) Erfinder; und (75) Erfinder/Anmelder (nur für US): DORSCH, Dieter [DE/DE]; Königsberger Strasse 17A, D-64372 Ober-Ramstadt (DE). JURASZYK, Horst [DE/DE]; Kleiner Ring 14, D-64342 Seeheim (DE). WURZIGER, Hanns [DE/DE]; Greinstrasse 7b, D-64291 Darmstadt (DE). BERNO- TAT-DANIELOWSKI, Sabine [DE/DE]; Liebigstrasse 5, D-61231 Bad Nauheim (DE). MELZER, Guido [AT/DE]; Mörkestrasse 6, D-65719 Hofheim (DE). (74) Gemeinsamer Vertreter: MERCK PATENT GMBH; D-64271 Darmstadt (DE).		(81) Bestimmungsstaaten: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO Patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Veröffentlicht <i>Mit internationalem Recherchenbericht.</i> <i>Vor Ablauf der für Änderungen der Ansprüche zugelassenen</i> <i>Frist; Veröffentlichung wird wiederholt falls Änderungen</i> <i>eintreffen.</i>	
(54) Title: BENZAMIDINE DERIVATIVES AS FACTOR XA INHIBITORS (54).Bezeichnung: BENZAMIDINDERIVATE ALS FAKTOR XA-INHIBITOREN			
<div style="text-align: center;"><p>(I)</p></div>			
(57) Abstract The invention relates to novel compounds of formula (I), wherein X, Y, R ¹ , R ² and R ³ have the meanings given in Claim 1, are inhibitors of coagulation factor Xa, and can be used for preventing or treating thromboembolic disorders. (57) Zusammenfassung Neue Verbindungen der Formel (I), worin X, Y, R ¹ und R ³ die im Patentanspruch 1 angegebene Bedeutung haben, sind Inhibitoren des Koagulationsfaktors Xa und können zur Prophylaxe und/oder Therapie von thromboembolischen Erkrankungen eingesetzt werden.			

LEDIGLICH ZUR INFORMATION

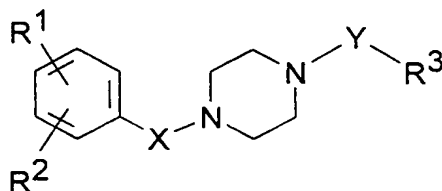
Codes zur Identifizierung von PCT-Vertragsstaaten auf den Kopfbögen der Schriften, die internationale Anmeldungen gemäss dem PCT veröffentlichen.

AL	Albanien	ES	Spanien	LS	Lesotho	SI	Slowenien
AM	Armenien	FI	Finnland	LT	Litauen	SK	Slowakei
AT	Österreich	FR	Frankreich	LU	Luxemburg	SN	Senegal
AU	Australien	GA	Gabun	LV	Lettland	SZ	Swasiland
AZ	Aserbaidshan	GB	Vereinigtes Königreich	MC	Monaco	TD	Tschad
BA	Bosnien-Herzegowina	GE	Georgien	MD	Republik Moldau	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagaskar	TJ	Tadschikistan
BE	Belgien	GN	Guinea	MK	Die ehemalige jugoslawische	TM	Turkmenistan
BF	Burkina Faso	GR	Griechenland		Republik Mazedonien	TR	Türkei
BG	Bulgarien	HU	Ungarn	ML	Mali	TT	Trinidad und Tobago
BJ	Benin	IE	Irland	MN	Mongolei	UA	Ukraine
BR	Brasilien	IL	Israel	MR	Mauritanien	UG	Uganda
BY	Belarus	IS	Island	MW	Malawi	US	Vereinigte Staaten von
CA	Kanada	IT	Italien	MX	Mexiko		Amerika
CF	Zentralafrikanische Republik	JP	Japan	NE	Niger	UZ	Usbekistan
CG	Kongo	KE	Kenia	NL	Niederlande	VN	Vietnam
CH	Schweiz	KG	Kirgisistan	NO	Norwegen	YU	Jugoslawien
CI	Côte d'Ivoire	KP	Demokratische Volksrepublik	NZ	Neuseeland	ZW	Zimbabwe
CM	Kamerun		Korea	PL	Polen		
CN	China	KR	Republik Korea	PT	Portugal		
CU	Kuba	KZ	Kasachstan	RO	Rumänien		
CZ	Tschechische Republik	LC	St. Lucia	RU	Russische Föderation		
DE	Deutschland	LI	Liechtenstein	SD	Sudan		
DK	Dänemark	LK	Sri Lanka	SE	Schweden		
EE	Estland	LR	Liberia	SG	Singapur		

BENZAMIDINDERIVATE ALS FAKTOR XA-INHIBITOREN

Die Erfindung betrifft Verbindungen der Formel I

5

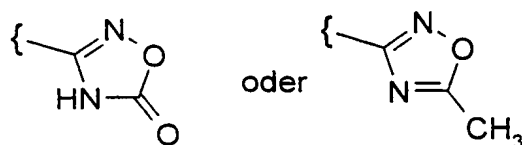


10

worin

R^1 $-C(=NH)-NH_2$, das auch einfach durch $-COA$, $-CO-[C(R^6)_2]_n-Ar$, $-COOA$, $-OH$ oder durch eine konventionelle Aminoschutzgruppe substituiert sein kann,

15



20

R^2 H , A , OR^6 , $N(R^6)_2$, NO_2 , CN , Hal , $NHCOA$, $NHCOAr$, $NHSO_2A$, $NHSO_2Ar$, $COOR^6$, $CON(R^6)_2$, $CONHAr$, COR^6 , $COAr$, $S(O)_nA$ oder $S(O)_nAr$,

25

R^3 A , Cycloalkyl, $-[C(R^6)_2]_nAr$, $-[C(R^6)_2]_n-O-Ar$, $-[C(R^6)_2]_nHet$ oder $-C(R^6)_2=C(R^6)_2-Ar$,

R^6 H , A oder Benzyl,

30

X fehlt, $-CO-$, $-C(R^6)_2-$, $-C(R^6)_2-C(R^6)_2-$, $-C(R^6)_2-CO-$, $-C(R^6)_2-C(R^6)_2-CO-$, $-C(R^6)=C(R^6)-CO-$, NR^6CO- , $-N\{[C(R^6)_2]_n-COOR^6\}-CO-$ oder $-C(COOR^6)R^6-C(R^6)_2-CO-$,

35

Y $-C(R^6)_2-$, $-SO_2-$, $-CO-$, $-COO-$ oder $-CONR^6-$,

- 5 A Alkyl mit 1-20 C-Atomen, worin eine oder zwei CH₂-Gruppen durch O- oder S-Atome oder durch -CR⁶=CR⁶-Gruppen und/oder 1-7 H-Atome durch F ersetzt sein können,
- 10 Ar unsubstituiertes oder ein-, zwei- oder dreifach durch A, Ar', OR⁶, N(R⁶)₂, NO₂, CN, Hal, NHCOA, NHCOAr', NHSO₂A, NHSO₂Ar', COOR⁶, CON(R⁶)₂, CONHAr', COR⁶, COAr', S(O)_nA oder S(O)_nAr substituiertes Phenyl oder Naphthyl,
- 15 Ar' unsubstituiertes oder ein-, zwei- oder dreifach durch A, OR⁶, N(R⁶)₂, NO₂, CN, Hal, NHCOA, COOR⁶, CON(R⁶)₂, COR⁶, oder S(O)_nA substituiertes Phenyl oder Naphthyl,
- 20 Het ein- oder zweikerniges unsubstituiertes oder ein- oder mehrfach durch Hal, A, Ar', COOR⁶, CN, N(R⁶)₂, NO₂, Ar-CONH-CH₂ und/oder Carbonylsauerstoff substituiertes gesättigtes oder ungesättigtes heterocyclisches Ringsystem, welches eines, zwei, drei oder vier gleiche oder verschiedene Heteroatome wie Stickstoff, Sauerstoff und Schwefel enthält,
- 25 Hal F, Cl, Br oder I,
- n 0, 1 oder 2 bedeutet,
- 30 sowie deren Salze.
- Gegenstand der Erfindung sind auch die optisch aktiven Formen, die Racemate, die Diastereomeren sowie die Hydrate und Solvate dieser Verbindungen.
- 35

Der Erfindung lag die Aufgabe zugrunde, neue Verbindungen mit wertvollen Eigenschaften aufzufinden, insbesondere solche, die zur Herstellung von Arzneimitteln verwendet werden können.

- 5 Es wurde gefunden, daß die Verbindungen der Formel I und ihre Salze bei guter Verträglichkeit sehr wertvolle pharmakologische Eigenschaften besitzen. Insbesondere zeigen sie Faktor Xa inhibierende Eigenschaften und können daher zur Bekämpfung und Verhütung von thromboembolischen Erkrankungen wie Thrombose, myocardialen Infarkt, Arteriosklerose, Entzündungen, Apoplexie, Angina pectoris, Restenose nach Angioplastie und
- 10 Claudicatio intermittens eingesetzt werden.

- Aromatische Amidinderivate mit antithrombotischer Wirkung sind z.B. aus der EP 0 540 051 B1 bekannt. Cyclische Guanidine zur Behandlung
- 15 thromboembolischer Erkrankungen sind z.B. in der WO 97/08165 beschrieben. Aromatische Heterocyclen mit Faktor Xa inhibitorischer Aktivität sind z.B. aus der WO 96/10022 bekannt.

- Der antithrombotische und antikoagulierende Effekt der erfindungsgemäßen Verbindungen wird auf die inhibierende Wirkung gegenüber der aktivierten Gerinnungsprotease, bekannt unter dem Namen Faktor Xa, zurückgeführt.
- 20

- Faktor Xa ist eine der Proteasen, die in den komplexen Vorgang der Blutgerinnung involviert ist. Faktor Xa katalysiert die Umwandlung von Prothrombin in Thrombin, das seinerseits zur Thrombusbildung beiträgt. Eine
- 25 Aktivierung von Thrombin kann zum Auftreten von thromboembolischen Erkrankungen führen.

- Eine Inhibierung des Faktors Xa kann somit verhindern, daß Thrombin gebildet wird.
- 30 Die erfindungsgemäßen Verbindungen der Formel I sowie ihre Salze greifen durch Inhibierung des Faktors Xa in den Blutgerinnungsprozeß ein und hemmen so die Entstehung von Thromben.

- Die Inhibierung des Faktors Xa durch die erfindungsgemäßen Verbindungen und die Messung der antikoagulierenden und antithrombotischen Aktivität kann nach üblichen in vitro- oder in vivo-Methoden ermittelt werden.
- 35

Ein geeignetes Verfahren wird z.B. von J. Hauptmann et al. in *Thrombosis and Haemostasis* 63, 220-223 (1990) beschrieben.

5 Die Messung der Inhibierung von Faktor Xa kann z.B. nach der Methode von T. Hara et al. in *Thromb. Haemostas.* 71, 314-319 (1994) erfolgen.

10 Die Verbindungen der Formel I können als Arzneimittelwirkstoffe in der Human- und Veterinärmedizin eingesetzt werden, insbesondere zur Bekämpfung und Verhütung von thromboembolischen Erkrankungen wie Thrombose, myocardialem Infarkt, Arteriosklerose, Entzündungen, Apoplexie, Angina pectoris, Restenose nach Angioplastie und Claudicatio intermittens.

15 Gegenstand der Erfindung sind die Verbindungen der Formel I und ihre Salze sowie ein Verfahren zur Herstellung von Verbindungen der Formel I nach Anspruch 1 sowie ihrer Salze, dadurch gekennzeichnet, daß man

20 a) sie aus einem ihrer funktionellen Derivate durch Behandeln mit einem solvolysierenden oder hydrogenolysierenden Mittel in Freiheit setzt, indem man

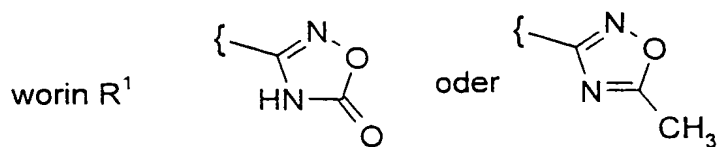
i) eine Amidinogruppe aus ihrem Oxadiazolderivat durch Hydrogenolyse freisetzt,

25 ii) eine konventionelle Aminoschutzgruppe durch Behandeln mit einem solvolysierenden oder hydrogenolysierenden Mittel durch Wasserstoff ersetzt oder eine durch eine konventionelle Schutzgruppe geschützte Aminogruppe in Freiheit setzt,

30 oder

b) daß man zur Herstellung von Verbindungen der Formel I,

35

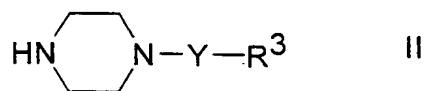


5

X -CO- oder -C(R⁶)₂-CO-,
und R², R³ und Y die in Anspruch 1 angegebenen Bedeutungen haben,

10

eine Verbindung der Formel II



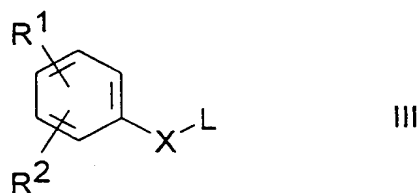
worin

15

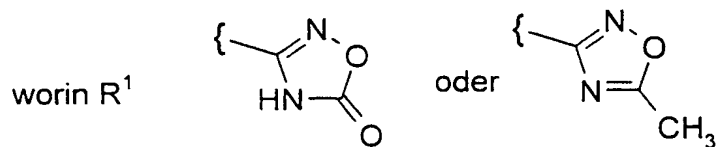
R³, R⁴, R⁵, W und Y die in Anspruch 1 angegebenen Bedeutungen haben,

mit einer Verbindung der Formel III

20



25



30

X -CO- oder -C(R⁶)₂-CO- bedeutet,

R² die in Anspruch 1 angegebene Bedeutung hat,

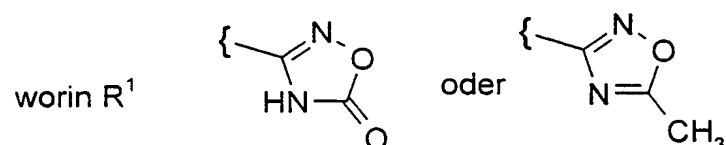
und L Cl, Br, I oder eine freie oder reaktionsfähig funktionell
abgewandelte OH-Gruppe bedeutet,

35

umsetzt,

oder

- 5 c) daß man zur Herstellung von Verbindungen der Formel I,



10

Y -SO₂-, -CO-, -COO- oder -C(R⁶)₂- bedeutet,
und R² und X die in Anspruch 1 angegebenen Bedeutungen haben,

eine Verbindung der Formel IV

15

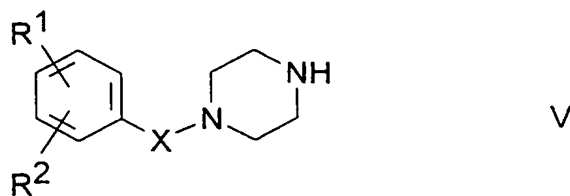


worin

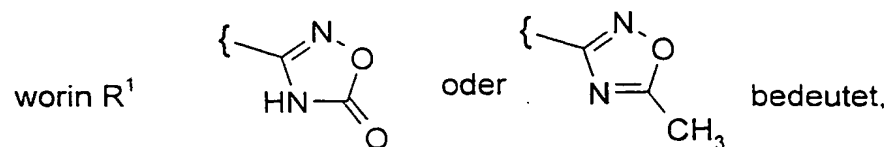
Y -SO₂-, -CO-, -COO- oder -C(R⁶)₂- bedeutet,
20 R³ die in Anspruch 1 angegebene Bedeutung hat, und L Cl, Br, I
oder eine freie oder reaktionsfähig funktionell abgewandelte
OH-Gruppe bedeutet,

mit einer Verbindung der Formel V

25



30



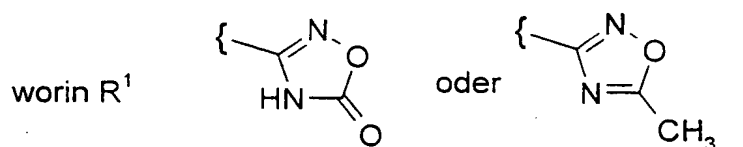
35

und R² und X die in Anspruch 1 angegebenen Bedeutungen haben,

umsetzt,

oder

5 d) daß man zur Herstellung von Verbindungen der Formel I,



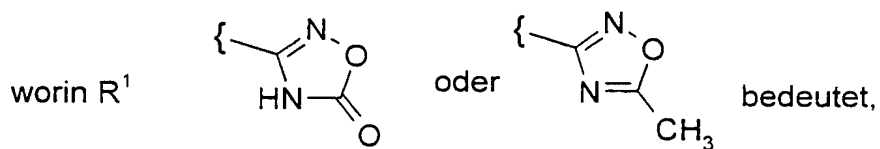
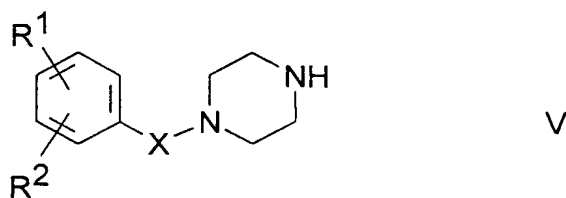
Y -CONH- bedeutet,
und R² und X die in Anspruch 1 angegebenen Bedeutungen haben,

15 eine Verbindung der Formel VI



worin R³ die in Anspruch 1 angegebene Bedeutung hat,

20 mit einer Verbindung der Formel V



und R² und X die in Anspruch 1 angegebenen Bedeutungen haben,

35 umsetzt,

oder

- e) daß man zur Herstellung von Verbindungen der Formel I,
worin R^1 $-C(=NH)-NH_2$ bedeutet,
5 eine Cyangruppe in eine Amidinogruppe umwandelt,
- f) und/oder daß man in einer Verbindung der Formel I einen oder mehrere Rest(e) R^1 , R^2 und/oder R^3 in einen oder mehrere Rest(e) R^1 , R^2
10 und/oder R^3 umwandelt,
indem man beispielsweise
- i) eine Estergruppe zu einer Carboxygruppe hydrolysiert,
15 ii) eine Nitrogruppe reduziert,
iii) eine Aminogruppe acyliert,
- g) und/oder eine Base oder Säure der Formel I in eines ihrer Salze umwandelt.
20
- Für alle Reste, die mehrfach auftreten, wie z.B. R^6 , gilt, daß deren Bedeutungen unabhängig voneinander sind.
25
- Vor- und nachstehend haben die Reste bzw. Parameter L, X, Y, R^1 , R^2 und R^3 die bei den Formeln I bis VI angegebenen Bedeutungen, falls nicht ausdrücklich etwas anderes angegeben ist.
- 30 In den vorstehenden Formeln bedeutet A Alkyl und hat 1 bis 20, vorzugsweise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 oder 12 C-Atome. A bedeutet vorzugsweise Methyl, weiterhin Ethyl, Propyl, Isopropyl, Butyl, Isobutyl, sek.-Butyl oder tert.-Butyl, ferner auch Pentyl, 1-, 2- oder 3-Methylbutyl, 1,1-, 1,2- oder 2,2-Dimethylpropyl, 1-Ethylpropyl, Hexyl, 1-, 2-, 3- oder 4-
35 Methylpentyl, 1,1-, 1,2-, 1,3-, 2,2-, 2,3- oder 3,3-Dimethylbutyl, 1- oder

2-Ethylbutyl, 1-Ethyl-1-methylpropyl, 1-Ethyl-2-methylpropyl, 1,1,2- oder 1,2,2-Trimethylpropyl, Heptyl, Octyl, Nonyl oder Decyl.

Alkyl bedeutet weiterhin z.B. Trifluormethyl, Pentafluorethyl, Allyl oder Crotyl.

5

Cycloalkyl bedeutet vorzugsweise Cyclopropyl, Cyclobutyl, Cylopentyl, Cyclohexyl oder Cycloheptyl. Cycloalkyl bedeutet insbesondere den Rest eines bicyclischen Terpens, wie z.B. 3-Menthyl, ganz besonders bevorzugt ist der Campher-10-yl-Rest.

10

COR⁶ ist Acyl und bedeutet vorzugsweise Formyl, Acetyl, Propionyl, ferner auch Butyryl, Pentanoyl oder Hexanoyl.

Hal bedeutet vorzugsweise F, Cl oder Br, aber auch I.

15

R² bedeutet vorzugsweise H, Fluor, Chlor, Brom, Iod, Hydroxy, Methoxy, Ethoxy, Propoxy, Nitro, Amino, Methylamino, Dimethylamino, Ethylamino, Diethylamino, Acetamido, Sulfonamido, Methylsulfonamido, Phenylsulfonamido, Methylthio, Ethylthio, Methylsulfinyl, Ethylsulfinyl, Methylsulfonyl, Ethylsulfonyl, Phenylsulfinyl, Phenylsulfonyl, Cyan, Carboxy, Methoxycarbonyl, Ethoxycarbonyl, ferner auch Acyl oder Benzoyl.

20

R³ bedeutet vorzugsweise z.B. A, Cycloalkyl, Ar, CH₂Ar, CH₂OAr, CH₂CH₂Ar, CH₂Het, CH₂CH₂Het oder CH=CH-Ar.

25

R⁶ bedeutet H, A oder Benzyl, insbesondere jedoch H.

X bedeutet vorzugsweise z.B. fehlt, -CO-, -CH₂-, -CH₂-CH₂-, -CH₂-CO-, -CH₂-CH₂-CO-, -CH=CH-CO-, NR⁶CO-, -N{[CH₂]_n-COOR⁶}-CO- oder -CH(COOR⁶)-CH₂-CO-.

30

Y bedeutet vorzugsweise z.B. -SO₂- oder -CO-, ferner auch -COO-, -CONH- oder -CH₂-.

35

Ar bedeutet vorzugsweise unsubstituiertes Phenyl oder Naphthyl, weiterhin vorzugsweise z.B. durch A, Fluor, Chlor, Brom, Iod, Hydroxy, Methoxy,

5 Ethoxy, Propoxy, Butoxy, Pentyloxy, Hexyloxy, Benzyloxy, Phenethyloxy, Methylthio, Ethylthio, Methylsulfinyl, Ethylsulfinyl, Methylsulfonyl, Ethylsulfonyl, Phenylsulfinyl, Phenylsulfonyl, Nitro, Amino, Methylamino, Ethylamino, Dimethylamino, Diethylamino, Formamido, Acetamido, Propionylamino, Butyrylamino, Methylsulfonamido, Ethylsulfonamido, Propylsulfonamido, Butylsulfonamido, Phenylsulfonamido, (4-Methylphenyl)-sulfonamido, Carboxymethoxy, Carboxyethoxy, Methoxycarbonylmethoxy, Methoxycarbonylethoxy, Hydroxymethoxy, Hydroxyethoxy, Methoxyethoxy, Carboxy, Methoxycarbonyl, Ethoxycarbonyl, Cyan, Phenylaminocarbonyl, 10 Acyl oder Benzoyl mono-, di- oder trisubstituiertes Phenyl oder Naphthyl, ferner auch Biphenyl.

Ar bedeutet daher bevorzugt z.B. o-, m- oder p-Tolyl, o-, m- oder p-Ethylphenyl, o-, m- oder p-Propylphenyl, o-, m- oder p-Isopropylphenyl, o-, m- oder p-tert.-Butylphenyl, o-, m- oder p-Hydroxyphenyl, o-, m- oder p-Nitrophenyl, o-, m- oder p-Aminophenyl, o-, m- oder p-(N-Methylamino)-phenyl, o-, m- oder p-Acetamidophenyl, o-, m- oder p-Methoxyphenyl, o-, m- oder p-Ethoxyphenyl, o-, m- oder p-Carboxyphenyl, o-, m- oder p-Methoxycarbonylphenyl, o-, m- oder p-(N,N-Dimethylamino)-phenyl, o-, m- oder p-(N-Ethylamino)-phenyl, o-, m- oder p-(N,N-Diethylamino)-phenyl, o-, m- oder p-Acetylphenyl, o-, m- oder p-Formylphenyl, o-, m- oder p-Fluorphenyl, o-, m- oder p-Bromphenyl, o-, m- oder p-Chlorphenyl, o-, m- oder p-Methylsulfonylphenyl, o-, m- oder p-(Phenylsulfonamido)-phenyl, o-, m- oder p-(Methylsulfonamido)-phenyl, o-, m- oder p-Methylthiophenyl, weiter bevorzugt 2,3-, 2,4-, 2,5-, 2,6-, 3,4- oder 3,5-Difluorphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- oder 3,5-Dichlorphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- oder 3,5-Dibromphenyl, 2,4- oder 2,5-Dinitrophenyl, 2,5- oder 3,4-Dimethoxyphenyl, 3-Nitro-4-chlorphenyl, 3-Amino-4-chlor-, 2-Amino-3-chlor-, 2-Amino-4-chlor-, 2-Amino-5-chlor- oder 2-Amino-6-chlorphenyl, 2-Nitro-4-N,N-dimethylamino- oder 3-Nitro-4-N,N-dimethylaminophenyl, 2,3-Diaminophenyl, 2,3,4-, 2,3,5-, 2,3,6-, 2,4,6- oder 3,4,5-Trichlorphenyl, 2,4,6-Trimethoxyphenyl, 2-Hydroxy-3,5-dichlorphenyl, p-Iodphenyl, 3,6-Dichlor-4-aminophenyl, 4-Fluor-3-chlorphenyl, 2-Fluor-4-bromphenyl, 2,5-Difluor-4-bromphenyl, 3-Brom-6-methoxyphenyl, 3-Chlor-6-methoxyphenyl, 3-Chlor-4-acetamidophenyl, 3-Fluor-4-methoxyphenyl, 3-Amino-6-methylphenyl, 3-Chlor-4-acetamidophenyl oder 2,5-Dimethyl-4-chlorphenyl.

Ar bedeutet ganz besonders bevorzugt unsubstituiertes Phenyl oder Naphthyl, weiterhin vorzugsweise z.B. durch A, Chlor, Methoxy, Amino, Dimethylamino mono-, di- oder trisubstituiertes Phenyl oder Naphthyl, ferner auch Biphenyl.

Ar' bedeutet insbesondere z.B. Phenyl oder Naphthyl, ferner bevorzugt z.B. o-, m- oder p-Tolyl, o-, m- oder p-Ethylphenyl, o-, m- oder p-Propylphenyl, o-, m- oder p-Isopropylphenyl, o-, m- oder p-tert.-Butylphenyl, o-, m- oder p-Hydroxyphenyl, o-, m- oder p-Nitrophenyl, o-, m- oder p-Aminophenyl, o-, m- oder p-(N-Methylamino)-phenyl, o-, m- oder p-Acetamidophenyl, o-, m- oder p-Methoxyphenyl, o-, m- oder p-Ethoxyphenyl, o-, m- oder p-Carboxyphenyl, o-, m- oder p-Methoxycarbonylphenyl, o-, m- oder p-(N,N-Dimethylamino)-phenyl, o-, m- oder p-(N-Ethylamino)-phenyl, o-, m- oder p-(N,N-Diethylamino)-phenyl, o-, m- oder p-Acetylphenyl, o-, m- oder p-Formylphenyl, o-, m- oder p-Fluorphenyl, o-, m- oder p-Bromphenyl, o-, m- oder p-Chlorphenyl oder o-, m- oder p-Methylsulfonylphenyl.

Het bedeutet vorzugsweise z.B. 2- oder 3-Furyl, 2- oder 3-Thienyl, 1-, 2- oder 3-Pyrrolyl, 1-, 2, 4- oder 5-Imidazolyl, 1-, 3-, 4- oder 5-Pyrazolyl, 2-, 4- oder 5-Oxazolyl, 3-, 4- oder 5-Isioxazolyl, 2-, 4- oder 5-Thiazolyl, 3-, 4- oder 5-Isouthiazolyl, 2-, 3- oder 4-Pyridyl, 2-, 4-, 5- oder 6-Pyrimidinyl, weiterhin bevorzugt 1,2,3-Triazol-1-, -4- oder -5-yl, 1,2,4-Triazol-1-, -3- oder -5-yl, 1- oder 5-Tetrazolyl, 1,2,3-Oxadiazol-4- oder -5-yl, 1,2,4-Oxadiazol-3- oder -5-yl, 1,3,4-Thiadiazol-2- oder -5-yl, 1,2,4-Thiadiazol-3- oder -5-yl, 1,2,3-Thiadiazol-4- oder -5-yl, 3- oder 4-Pyridazinyl, Pyrazinyl, 1-, 2-, 3-, 4-, 5-, 6- oder 7-Indolyl, 4- oder 5-Isoindolyl, 1-, 2-, 4- oder 5-Benzimidazolyl, 1-, 3-, 4-, 5-, 6- oder 7-Benzopyrazolyl, 2-, 4-, 5-, 6- oder 7-Benzoxazolyl, 3-, 4-, 5-, 6- oder 7-Benzisoxazolyl, 2-, 4-, 5-, 6- oder 7-Benzothiazolyl, 2-, 4-, 5-, 6- oder 7-Benzisothiazolyl, 4-, 5-, 6- oder 7-Benz-2,1,3-oxadiazolyl, 2-, 3-, 4-, 5-, 6-, 7- oder 8-Chinolyl, 1-, 3-, 4-, 5-, 6-, 7- oder 8-Isochinolyl, 3-, 4-, 5-, 6-, 7- oder 8-Cinnolyl, 2-, 4-, 5-, 6-, 7- oder 8-Chinazolinyl, 5- oder 6-Chinoxalyl, 2-, 3-, 5-, 6-, 7- oder 8-2H-Benzo[1,4]oxazinyl, weiter bevorzugt 1,3-Benzodioxol-5-yl, 1,4-Benzodioxan-6-yl, 2,1,3-Benzothiadiazol-4- oder -5-yl, 2,1,3-Benzoxadiazol-5-yl oder Dibenzofuranyl.

Die heterocyclischen Reste können auch teilweise oder vollständig hydriert sein.

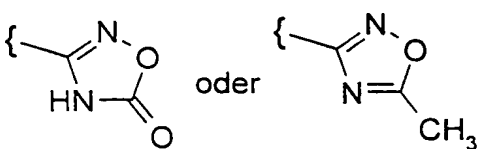
Het kann also z. B. auch bedeuten 2,3-Dihydro-2-, -3-, -4- oder -5-furyl, 2,5-Dihydro-2-, -3-, -4- oder 5-furyl, Tetrahydro-2- oder -3-furyl, 1,3-Dioxolan-4-yl, Tetrahydro-2- oder -3-thienyl, 2,3-Dihydro-1-, -2-, -3-, -4- oder -5-pyrrolyl, 2,5-Dihydro-1-, -2-, -3-, -4- oder -5-pyrrolyl, 1-, 2- oder 3-Pyrrolidinyl, Tetrahydro-1-, -2- oder -4-imidazolyl, 2,3-Dihydro-1-, -2-, -3-, -4- oder -5-pyrazolyl, Tetrahydro-1-, -3- oder -4-pyrazolyl, 1,4-Dihydro-1-, -2-, -3- oder -4-pyridyl, 1,2,3,4-Tetrahydro-1-, -2-, -3-, -4-, -5- oder -6-pyridyl, 1-, 2-, 3- oder 4-Piperidiny, 2-, 3- oder 4-Morpholinyl, Tetrahydro-2-, -3- oder -4-pyranyl, 1,4-Dioxanyl, 1,3-Dioxan-2-, -4- oder -5-yl, Hexahydro-1-, -3- oder -4-pyridazinyl, Hexahydro-1-, -2-, -4- oder -5-pyrimidinyl, 1-, 2- oder 3-Piperazinyl, 1,2,3,4-Tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- oder -8-chinoly, 1,2,3,4-Tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- oder -8-isochinoly, 2-, 3-, 5-, 6-, 7- oder 8- 3,4-Dihydro-2H-benzo[1,4]oxazinyl, weiter bevorzugt 2,3-Methylenedioxyphenyl, 3,4-Methylenedioxyphenyl, 2,3-Ethylendioxyphenyl, 3,4-Ethylendioxyphenyl, 3,4-(Difluormethylenedioxy)phenyl, 2,3-Dihydrobenzofuran-5- oder 6-yl, 2,3-(2-Oxo-methylenedioxy)-phenyl oder auch 3,4-Dihydro-2H-1,5-benzodioxepin-6- oder -7-yl, ferner bevorzugt 2,3-Dihydrobenzofuranyl oder 2,3-Dihydro-2-oxo-furanyl.

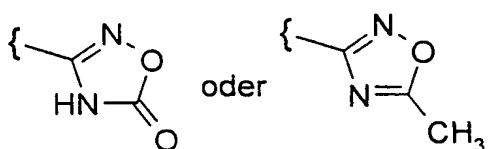
Het ist unsubstituiert oder ein- oder mehrfach durch Hal, A, Ar', COOR⁶, CN, N(R⁶)₂, NO₂, Ar-CONH-CH₂ substituiert.

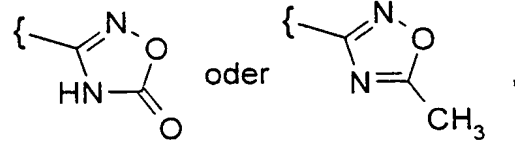
"Mehrfach" bedeutet zwei-, drei-, vier- oder fünffach.

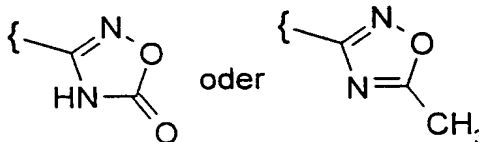
Die Verbindungen der Formel I können ein oder mehrere chirale Zentren besitzen und daher in verschiedenen stereoisomeren Formen vorkommen. Die Formel I umschließt alle diese Formen.

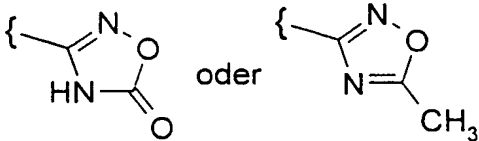
Dementsprechend sind Gegenstand der Erfindung insbesondere diejenigen Verbindungen der Formel I, in denen mindestens einer der genannten Reste eine der vorstehend angegebenen bevorzugten Bedeutungen hat. Einige bevorzugte Gruppen von Verbindungen können durch die folgenden Teilformeln Ia bis If ausgedrückt werden, die der Formel I entsprechen und worin die nicht näher bezeichneten Reste die bei der Formel I angegebene Bedeutung haben, worin jedoch

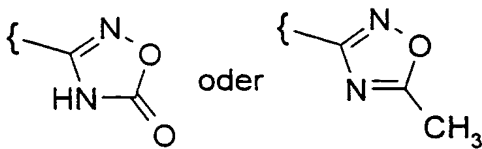
5	in Ia R ¹	-C(=NH)-NH ₂ , das auch einfach durch -COA, -CO-[C(R ⁶) ₂] _n -Ar, -COOA, -OH oder durch eine konventionelle Aminoschutzgruppe substituiert sein kann,
		
10	R ²	H, A, OR ⁶ , N(R ⁶) ₂ , NO ₂ , CN, Hal, NHCOA, NHCOAr, NHSO ₂ A, NHSO ₂ Ar, COOR ⁶ , CON(R ⁶) ₂ , CONHAr, COR ⁶ , COAr, S(O) _n A oder S(O) _n Ar,
	R ³	A, Cycloalkyl, Ar, CH ₂ Ar, CH ₂ OAr, CH ₂ CH ₂ Ar, CH ₂ Het, CH ₂ CH ₂ Het oder CH=CH-Ar,
15	R ⁶	H oder A,
	X	fehlt, -CO-, -CH ₂ -CO-, -CH ₂ -CH ₂ -CO-, -CH ₂ -, -CH ₂ -CH ₂ -, -CH=CH-CO-, -NHCO-, -N(CH ₂ COOR ⁶)-CO- oder -CH(COOR ⁶)-CH ₂ -CO-,
20	Y	-SO ₂ -, -CO-, -COO-, -CO-NH- oder -CH ₂ -,
	A	Alkyl mit 1-20 C-Atomen, worin eine oder zwei CH ₂ -Gruppen durch O- oder S-Atome oder durch -CR ⁶ =CR ⁶ -Gruppen und/oder 1-7 H-Atome durch F ersetzt sein können,
25	Ar	unsubstituiertes oder ein-, zwei- oder dreifach durch A, Ar', OR ⁶ , N(R ⁶) ₂ , NO ₂ , CN, Hal, NHCOA, NHCOAr', NHSO ₂ A, NHSO ₂ Ar', COOR ⁶ , CON(R ⁶) ₂ , CONHAr', COR ⁶ , COAr', S(O) _n A oder S(O) _n Ar substituiertes Phenyl oder Naphthyl,
30	Ar'	unsubstituiertes oder ein-, zwei- oder dreifach durch A, OR ⁶ , N(R ⁶) ₂ , NO ₂ , CN, Hal, NHCOA, COOR ⁶ , CON(R ⁶) ₂ , COR ⁶ , oder S(O) _n A substituiertes Phenyl oder Naphthyl,
35	Het	ein- oder zweikerniges unsubstituiertes oder ein- oder mehrfach durch Hal, A, Ar', COOR ⁶ , CN, N(R ⁶) ₂ , NO ₂ , Ar-CONH-CH ₂ und/oder Carbonylsauerstoff substitu-

			iertes gesättigtes oder ungesättigtes heterocyclisches Ringsystem, welches eines, zwei, drei oder vier gleiche oder verschiedene Heteroatome wie Stickstoff, Sauerstoff und Schwefel enthält,
5	Hal		F, Cl, Br oder I und
	n		0, 1 oder 2
	bedeutet;		
	in lb	R ¹	-C(=NH)-NH ₂ , das auch einfach durch -COA,
10			-CO-[C(R ⁶) ₂] _n -Ar, -COOA, -OH oder durch eine konventionelle Aminoschutzgruppe substituiert sein kann,
15			
	R ²	H,	
	R ³	A, Cycloalkyl, Ar, -CH ₂ Ar, -CH ₂ OAr, -CH ₂ CH ₂ Ar, -CH ₂ Het, -CH ₂ CH ₂ Het oder -CH=CH-Ar,	
20	R ⁶	H oder A,	
	X	fehlt, -CO-, -CH ₂ -CO-, -CH ₂ -CH ₂ -CO-, -CH ₂ -, -CH ₂ -CH ₂ -, -CH=CH-CO-, -NHCO-, -N(CH ₂ COOR ⁶)-CO- oder -CH(COOR ⁶)-CH ₂ -CO-,	
25	Y	-SO ₂ -, -CO-, -COO-, -CO-NH- oder -CH ₂ -,	
	A	Alkyl mit 1-20 C-Atomen, worin eine oder zwei CH ₂ -Gruppen durch O- oder S-Atome oder durch -CR ⁶ =CR ⁶ -Gruppen und/oder 1-7 H-Atome durch F ersetzt sein können,	
30	Ar	unsubstituiertes oder ein-, zwei- oder dreifach durch A, Ar', OR ⁶ , NH ₂ , NO ₂ , CN, Hal, NHCOA, NHCOAr', NHSO ₂ A, NHSO ₂ Ar', COOR ⁶ , CON(R ⁶) ₂ , CONHAr', COR ⁶ , COAr', S(O) _n A oder S(O) _n Ar substituiertes Phenyl oder Naphthyl,	
35	Ar'	unsubstituiertes oder ein-, zwei- oder dreifach durch A, OR ⁶ , N(R ⁶) ₂ , NO ₂ , CN, Hal, NHCOA, COOR ⁶ ,	

5	Het	<p>CON(R⁶)₂, COR⁶, oder S(O)_nA substituiertes Phenyl oder Naphthyl,</p> <p>ein- oder zweikerniges unsubstituiertes oder ein- oder mehrfach durch Hal, A, Ar', COOR⁶, CN, N(R⁶)₂, NO₂, Ar-CONH-CH₂ und/oder Carbonylsauerstoff substituiertes gesättigtes oder ungesättigtes heterocyclisches Ringsystem, welches eines, zwei, drei oder vier gleiche oder verschiedene Heteroatome wie Stickstoff, Sauerstoff und Schwefel enthält,</p>
10	Hal n bedeutet;	<p>F, Cl, Br oder I und</p> <p>0, 1 oder 2</p>
15	in Ic	<p>R¹</p> <p>-C(=NH)-NH₂, das auch einfach durch -COA, -CO-[C(R⁶)₂]_n-Ar, -COOA, -OH oder durch eine konventionelle Aminoschutzgruppe substituiert sein kann,</p>
20		
25	R ² R ³	<p>H,</p> <p>A, Cycloalkyl, Ar, -CH₂Ar, -CH₂OAr, -CH₂CH₂Ar, -CH₂Het, -CH₂CH₂Het oder -CH=CH-Ar,</p>
30	R ⁶ X	<p>H oder A,</p> <p>fehlt, -CO-, -CH₂-CO-, -CH₂-CH₂-CO-, -CH₂-, -CH₂-CH₂-, -CH=CH-CO-, -NHCO-, -N{CH₂-COOR⁶}-CO- oder -CH(COOR⁶)-CH₂-CO-,</p>
35	Y A	<p>-SO₂-, -CO-, -COO-, -CO-NH- oder -CH₂-,</p> <p>Alkyl mit 1-20 C-Atomen, worin eine oder zwei CH₂-Gruppen durch O- oder S-Atome oder durch -CR⁶=CR⁶-Gruppen und/oder 1-7 H-Atome durch F ersetzt sein können,</p>

5	Ar	unsubstituiertes oder ein-, zwei- oder dreifach durch A, Ar', OR ⁶ , N(R ⁶) ₂ , NO ₂ , CN, Hal, NHCOA, NHCOAr', NHSO ₂ A, NHSO ₂ Ar', COOR ⁶ , CON(R ⁶) ₂ , CONHAr', COR ⁶ , COAr', S(O) _n A oder S(O) _n Ar substituiertes Phenyl oder Naphthyl,
10	Ar'	unsubstituiertes oder ein-, zwei- oder dreifach durch A, OR ⁶ , N(R ⁶) ₂ , NO ₂ , CN, Hal, NHCOA, COOR ⁶ , CON(R ⁶) ₂ , COR ⁶ , oder S(O) _n A substituiertes Phenyl oder Naphthyl,
15	Het	ein- oder zweikerniger unsubstituierter oder ein- oder mehrfach durch Hal, A, Ar', COOR ⁶ , CN, N(R ⁶) ₂ , NO ₂ , Ar-CONH-CH ₂ und/oder Carbonylsauerstoff substituiertes heterocyclisches Ringsystem ausgewählt aus der Gruppe
	Hal n bedeutet;	Thiophen, Tetrahydrochinolin, Chroman, Pyrazol, Isoxazol, Pyridin, Benzodioxol oder Benzothiophen, F, Cl, Br oder I und 0, 1 oder 2
20	in Id R ¹	-C(=NH)-NH ₂ , das auch einfach durch -COA, -CO-[C(R ⁶) ₂] _n -Ar, -COOA, -OH oder durch eine konventionelle Aminoschutzgruppe substituiert sein kann,
25		
30	R ² R ³	H, A, Cycloalkyl, Ar, -CH ₂ Ar, -CH ₂ OAr, -CH ₂ CH ₂ Ar, -CH ₂ Het, -CH ₂ CH ₂ Het oder -CH=CH-Ar,
35	R ⁶ X	H oder A, fehlt, -CO-, -CH ₂ -CO-, -CH ₂ -CH ₂ -CO-, -CH ₂ -, -CH ₂ -CH ₂ -, -CH=CH-CO-, -NHCO-, -N{CH ₂ -COOR ⁶ }-CO- oder -CH(COOR ⁶)-CH ₂ -CO-,

	Y	-SO ₂ -, -CO-, -CO-NH- oder -CH ₂ -,
	A	Alkyl mit 1-20 C-Atomen, worin eine oder zwei CH ₂ -Gruppen durch O- oder S-Atome oder durch -CR ⁶ =CR ⁶ -Gruppen und/oder 1-7 H-Atome durch F ersetzt sein können,
5	Ar	unsubstituiertes oder ein-, zwei- oder dreifach durch A, Ar', OR ⁶ , N(R ⁶) ₂ , NO ₂ , CN, Hal, NHCOA, NHCOAr', NHSO ₂ A, NHSO ₂ Ar', COOR ⁶ , CON(R ⁶) ₂ , CONHAr', COR ⁶ , COAr', S(O) _n A oder S(O) _n Ar substituiertes Phenyl oder Naphthyl,
10	Ar'	Phenyl,
	Het	ein- oder zweikerniger unsubstituierter oder ein- oder mehrfach durch Hal, A, Ar', COOR ⁶ , CN, N(R ⁶) ₂ , NO ₂ , Ar-CONH-CH ₂ und/oder Carbonylsauerstoff substituiertes heterocyclisches Ringsystem ausgewählt aus der Gruppe
15		Thiophen, Tetrahydrochinolin, Chroman, Pyrazol, Isoxazol, Pyridin, Benzodioxol, Benzothiophen oder Dibenzofuran,
20	Hal	F, Cl, Br oder I und
	n	0, 1 oder 2
		bedeutet;
	in le R ¹	-C(=NH)-NH ₂ , das auch einfach durch -COA,
25		-CO-[C(R ⁶) ₂] _n -Ar, -COOA, -OH oder durch eine konventionelle Aminoschutzgruppe substituiert sein kann,
30		
	R ²	H,
	R ³	A, Cycloalkyl, Ar, -CH ₂ Ar, -CH ₂ OAr, -CH ₂ CH ₂ Ar, -CH ₂ Het, -CH ₂ CH ₂ Het oder -CH=CH-Ar,
35	R ⁶	H oder A,
	X	fehlt, -CO-, -CH ₂ -CO-, -CH ₂ -CH ₂ -CO-, -CH ₂ -

			-CH ₂ -CH ₂ -, -NHCO-, -N{CH ₂ -COOR ⁶ }-CO- oder -CH(COOR ⁶)-CH ₂ -CO-,
	Y		-SO ₂ -, -CO- oder -CH ₂ -,
5	A		Alkyl mit 1-20 C-Atomen, worin eine oder zwei CH ₂ - Gruppen durch O- oder S-Atome oder durch -CR ⁶ =CR ⁶ -Gruppen und/oder 1-7 H-Atome durch F ersetzt sein können,
10	Ar		unsubstituiertes oder ein-, zwei- oder dreifach durch A, Ar', OR ⁶ , N(R ⁶) ₂ , NO ₂ , CN, Hal, NHCOA, NHCOAr', NHSO ₂ A, NHSO ₂ Ar', COOR ⁶ , CON(R ⁶) ₂ , CONHAr', COR ⁶ , COAr', S(O) _n A oder S(O) _n Ar substi- tuiertes Phenyl oder Naphthyl,
	Ar'		Phenyl,
15	Het		ein- oder zweikerniger unsubstituierter oder ein- oder mehrfach durch Hal, A, Ar', COOR ⁶ , CN, N(R ⁶) ₂ , NO ₂ , Ar-CONH-CH ₂ und/oder Carbonylsauerstoff substitu- iertes heterocyclisches Ringsystem ausgewählt aus der Gruppe
20			Thiophen, Tetrahydrochinolin, Chroman, Pyrazol, Isoxazol, Pyridin, Benzodioxol, Benzothiophen oder Dibenzofuran,
	Hal		F, Cl, Br oder I und
	n		0, 1 oder 2
			bedeutet;
25	in If	R ¹	-C(=NH)-NH ₂ , das auch einfach durch COOA substi- tuiert sein kann,
30			
	R ²		H,
	R ³		A, Cycloalkyl, Ar, -CH ₂ Ar, -CH ₂ OAr, -CH ₂ CH ₂ Ar, -CH ₂ Het, -CH ₂ CH ₂ Het oder -CH=CH-Ar,
35	R ⁶		H oder A,
	X		fehlt, -CO-, -CH ₂ -CO-, -CH ₂ -CH ₂ -CO-, -CH ₂ -,

		-CH ₂ -CH ₂ -, -NHCO-, -N{CH ₂ -COOR ⁶ }-CO- oder -CH(COOR ⁶)-CH ₂ -CO-,
	Y	-SO ₂ -, -CO- oder -CH ₂ -,
5	A	Alkyl mit 1-20 C-Atomen, worin eine oder zwei CH ₂ - Gruppen durch O- oder S-Atome oder durch -CR ⁶ =CR ⁶ -Gruppen und/oder 1-7 H-Atome durch F ersetzt sein können,
10	Ar	unsubstituiertes oder ein-, zwei- oder dreifach durch A, Ar', OR ⁶ , N(R ⁶) ₂ , NO ₂ , CN, Hal, NHCOA, NHCOAr', NHSO ₂ A, NHSO ₂ Ar', COOR ⁶ , CON(R ⁶) ₂ , CONHAr', COR ⁶ , COAr', S(O) _n A oder S(O) _n Ar substi- tuiertes Phenyl oder Naphthyl,
	Ar'	Phenyl,
15	Het	ein- oder zweikerniger unsubstituierter oder ein- oder mehrfach durch Hal, A, Ar', COOR ⁶ , CN, N(R ⁶) ₂ , NO ₂ , Ar-CONH-CH ₂ und/oder Carbonylsauerstoff substitu- iertes heterocyclisches Ringsystem ausgewählt aus der Gruppe
20		Thiophen, Tetrahydrochinolin, Chroman, Pyrazol, Isoxazol, Pyridin, Benzodioxol, Benzothiophen oder Dibenzofuran,
	Hal	F, Cl, Br oder I und
	n	0, 1 oder 2
		bedeutet.

25 Die Verbindungen der Formel I und auch die Ausgangsstoffe zu ihrer Herstellung werden im übrigen nach an sich bekannten Methoden hergestellt, wie sie in der Literatur (z.B. in den Standardwerken wie Houben-Weyl, Methoden der organischen Chemie, Georg-Thieme-Verlag, Stuttgart) be-

30 beschrieben sind, und zwar unter Reaktionsbedingungen, die für die genannten Umsetzungen bekannt und geeignet sind. Dabei kann man auch von an sich bekannten, hier nicht näher erwähnten Varianten Gebrauch machen.

35

Die Ausgangsstoffe können, falls erwünscht, auch in situ gebildet werden, so daß man sie aus dem Reaktionsgemisch nicht isoliert, sondern sofort weiter zu den Verbindungen der Formel I umsetzt.

- 5 Verbindungen der Formel I können vorzugsweise erhalten werden, indem man Verbindungen der Formel I aus einem ihrer funktionellen Derivate durch Behandeln mit einem solvolysierenden oder hydrogenolysierenden Mittel in Freiheit setzt.
- 10 Bevorzugte Ausgangsstoffe für die Solvolyse bzw. Hydrogenolyse sind solche, die sonst der Formel I entsprechen, aber anstelle einer oder mehrerer freier Amino- und/oder Hydroxygruppen entsprechende geschützte Amino- und/oder Hydroxygruppen enthalten, vorzugsweise solche, die an-
- 15 stelle eines H-Atoms, das mit einem N-Atom verbunden ist, eine Aminoschutzgruppe tragen, insbesondere solche, die anstelle einer HN-Gruppe eine R'-N-Gruppe tragen, worin R' eine Aminoschutzgruppe bedeutet, und/oder solche, die anstelle des H-Atoms einer Hydroxygruppe eine Hydroxyschutzgruppe tragen, z.B. solche, die der Formel I entsprechen, jedoch anstelle einer Gruppe -COOH eine Gruppe -COOR" tragen, worin
- 20 R" eine Hydroxyschutzgruppe bedeutet.
Bevorzugte Ausgangsstoffe sind auch die Oxadiazolderivate, die in die entsprechenden Amidinoverbindungen überführt werden können.
- 25 Die Einführung der Oxadiazolgruppe gelingt z.B. durch Umsetzung der Cyanverbindungen mit Hydroxylamin und Reaktion mit Phosgen, Dialkylcarbonat, Chlorameisensäureester, N,N'-Carbonyldiimidazol oder Acetanhydrid.
- 30 Es können auch mehrere - gleiche oder verschiedene - geschützte Amino- und/oder Hydroxygruppen im Molekül des Ausgangsstoffes vorhanden sein. Falls die vorhandenen Schutzgruppen voneinander verschieden sind, können sie in vielen Fällen selektiv abgespalten werden.
- 35 Der Ausdruck "Aminoschutzgruppe" ist allgemein bekannt und bezieht sich auf Gruppen, die geeignet sind, eine Aminogruppe vor chemischen Umsetzungen zu schützen (zu blockieren), die aber leicht entfernbar sind,

nachdem die gewünschte chemische Reaktion an anderen Stellen des Moleküls durchgeführt worden ist. Typisch für solche Gruppen sind insbesondere unsubstituierte oder substituierte Acyl-, Aryl-, Aralkoxymethyl- oder Aralkylgruppen. Da die Aminoschutzgruppen nach der gewünschten Reaktion (oder Reaktionsfolge) entfernt werden, ist ihre Art und Größe im übrigen nicht kritisch; bevorzugt werden jedoch solche mit 1-20, insbesondere 1-8 C-Atomen. Der Ausdruck "Acylgruppe" ist im Zusammenhang mit dem vorliegenden Verfahren in weitestem Sinne aufzufassen. Er umschließt von aliphatischen, araliphatischen, aromatischen oder heterocyclischen Carbonsäuren oder Sulfonsäuren abgeleitete Acylgruppen sowie insbesondere Alkoxycarbonyl-, Aryloxycarbonyl- und vor allem Aralkoxycarbonylgruppen. Beispiele für derartige Acylgruppen sind Alkanoyl wie Acetyl, Propionyl, Butyryl; Aralkanoyl wie Phenylacetyl; Aroyl wie Benzoyl oder Toluyl; Aryloxyalkanoyl wie POA; Alkoxycarbonyl wie Methoxycarbonyl, Ethoxycarbonyl, 2,2,2-Trichlorethoxycarbonyl, BOC (tert.-Butyloxycarbonyl), 2-Iodethoxycarbonyl; Aralkyloxycarbonyl wie CBZ ("Carbobenzoxy"), 4-Methoxybenzyloxycarbonyl, Fmoc; Arylsulfonyl wie Mtr. Bevorzugte Aminoschutzgruppen sind BOC und Mtr, ferner CBZ, Fmoc, Benzyl und Acetyl.

Der Ausdruck "Hydroxyschutzgruppe" ist ebenfalls allgemein bekannt und bezieht sich auf Gruppen, die geeignet sind, eine Hydroxygruppe vor chemischen Umsetzungen zu schützen, die aber leicht entfernbar sind, nachdem die gewünschte chemische Reaktion an anderen Stellen des Moleküls durchgeführt worden ist. Typisch für solche Gruppen sind die oben genannten unsubstituierten oder substituierten Aryl-, Aralkyl- oder Acylgruppen, ferner auch Alkylgruppen. Die Natur und Größe der Hydroxyschutzgruppen ist nicht kritisch, da sie nach der gewünschten chemischen Reaktion oder Reaktionsfolge wieder entfernt werden; bevorzugt sind Gruppen mit 1-20, insbesondere 1-10 C-Atomen. Beispiele für Hydroxyschutzgruppen sind u.a. Benzyl, p-Nitrobenzoyl, p-Toluolsulfonyl, tert.-Butyl und Acetyl, wobei Benzyl und tert.-Butyl besonders bevorzugt sind.

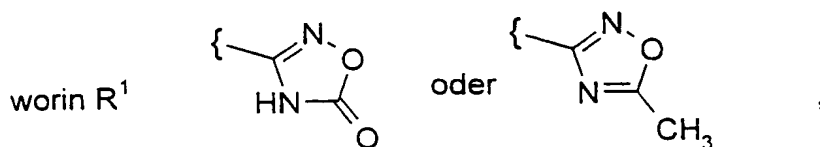
Das In-Freiheit-Setzen der Verbindungen der Formel I aus ihren funktionellen Derivaten gelingt - je nach der benutzten Schutzgruppe - z. B. mit starken Säuren, zweckmäßig mit TFA oder Perchlorsäure, aber auch mit an-

deren starken anorganischen Säuren wie Salzsäure oder Schwefelsäure, starken organischen Carbonsäuren wie Trichloressigsäure oder Sulfonsäuren wie Benzol- oder p-Toluolsulfonsäure. Die Anwesenheit eines zusätzlichen inerten Lösungsmittels ist möglich, aber nicht immer erforderlich. Als inerte Lösungsmittel eignen sich vorzugsweise organische, beispielsweise Carbonsäuren wie Essigsäure, Ether wie Tetrahydrofuran oder Dioxan, Amide wie DMF, halogenierte Kohlenwasserstoffe wie Dichlormethan, ferner auch Alkohole wie Methanol, Ethanol oder Isopropanol, sowie Wasser. Ferner kommen Gemische der vorgenannten Lösungsmittel in Frage. TFA wird vorzugsweise im Überschuß ohne Zusatz eines weiteren Lösungsmittels verwendet, Perchlorsäure in Form eines Gemisches aus Essigsäure und 70 %iger Perchlorsäure im Verhältnis 9:1. Die Reaktionstemperaturen für die Spaltung liegen zweckmäßig zwischen etwa 0 und etwa 50°, vorzugsweise arbeitet man zwischen 15 und 30° (Raumtemperatur).

Die Gruppen BOC, OBut und Mtr können z. B. bevorzugt mit TFA in Dichlormethan oder mit etwa 3 bis 5n HCl in Dioxan bei 15-30° abgespalten werden, die FMOC-Gruppe mit einer etwa 5- bis 50 %igen Lösung von Dimethylamin, Diethylamin oder Piperidin in DMF bei 15-30°.

Hydrogenolytisch entfernbare Schutzgruppen (z. B. CBZ, Benzyl oder die Freisetzung der Amidinogruppe aus ihrem Oxadiazolderivat)) können z. B. durch Behandeln mit Wasserstoff in Gegenwart eines Katalysators (z. B. eines Edelmetallkatalysators wie Palladium, zweckmäßig auf einem Träger wie Kohle) abgespalten werden. Als Lösungsmittel eignen sich dabei die oben angegebenen, insbesondere z. B. Alkohole wie Methanol oder Ethanol oder Amide wie DMF. Die Hydrogenolyse wird in der Regel bei Temperaturen zwischen etwa 0 und 100° und Drucken zwischen etwa 1 und 200 bar, bevorzugt bei 20-30° und 1-10 bar durchgeführt. Eine Hydrogenolyse der CBZ-Gruppe gelingt z. B. gut an 5 bis 10 %igem Pd/C in Methanol oder mit Ammoniumformiat (anstelle von Wasserstoff) an Pd/C in Methanol/DMF bei 20-30°.

Verbindungen der Formel I,



5 X -CO- oder -C(R⁶)₂-CO-,
und R², R³ und Y die in Anspruch 1 angegebenen Bedeutungen haben,
können vorzugsweise erhalten werden, indem man Verbindungen der
Formel II mit Verbindungen der Formel III umsetzt.

10 In den Verbindungen der Formel III bedeutet L vorzugsweise Cl, Br, I oder
eine reaktionsfähig abgewandelte OH-Gruppe wie z.B. ein aktivierter
Ester, ein Imidazolid oder Alkylsulfonyloxy mit 1-6 C-Atomen (bevorzugt
Methylsulfonyloxy) oder Arylsulfonyloxy mit 6-10 C-Atomen (bevorzugt
Phenyl- oder p-Tolylsulfonyloxy).

15 Die Umsetzung erfolgt in der Regel in einem inerten Lösungsmittel, in Ge-
genwart eines säurebindenden Mittels vorzugsweise eines Alkali- oder Er-
dalkalimetall-hydroxids, -carbonats oder -bicarbonats oder eines anderen
Salzes einer schwachen Säure der Alkali- oder Erdalkalimetalle, vorzugs-
weise des Kaliums, Natriums, Calciums oder Cäsiums. Auch der Zusatz
20 einer organischen Base wie Triethylamin, Dimethylanilin, Pyridin oder
Chinolin oder eines Überschusses der Aminkomponente der Formel II
bzw. des Alkylierungsderivates der Formel III kann günstig sein. Die Reak-
tionszeit liegt je nach den angewendeten Bedingungen zwischen einigen
Minuten und 14 Tagen, die Reaktionstemperatur zwischen etwa 0° und
25 150°, normalerweise zwischen 20° und 130°.

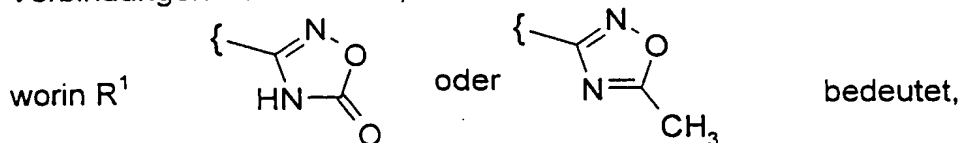
Als inerte Lösungsmittel eignen sich z.B. Kohlenwasserstoffe wie Hexan,
Petrolether, Benzol, Toluol oder Xylol; chlorierte Kohlenwasserstoffe wie
Trichlorethylen, 1,2-Dichlorethan, Tetrachlorkohlenstoff, Chloroform oder
30 Dichlormethan; Alkohole wie Methanol, Ethanol, Isopropanol, n-Propanol,
n-Butanol oder tert.-Butanol; Ether wie Diethylether, Diisopropylether,
Tetrahydrofuran (THF) oder Dioxan; Glykolether wie Ethylenglykolmono-
methyl- oder -monoethylether (Methylglykol oder Ethylglykol), Ethylen-
glykoldimethylether (Diglyme); Ketone wie Aceton oder Butanon; Amide
35 wie Acetamid, Dimethylacetamid, N-Methylpyrrolidon (NMP) oder Dime-
thylformamid (DMF); Nitrile wie Acetonitril; Sulfoxide wie Dimethylsulfoxid

(DMSO); Schwefelkohlenstoff; Carbonsäuren wie Ameisensäure oder Essigsäure; Nitroverbindungen wie Nitromethan oder Nitrobenzol; Ester wie Ethylacetat oder Gemische der genannten Lösungsmittel.

- 5 Die Ausgangsverbindungen der Formel II und III sind in der Regel bekannt. Sind sie neu, so können aber nach an sich bekannten Methoden hergestellt werden.

Verbindungen der Formel I,

10



- 15 Y SO₂, CO oder COO bedeutet,
und R² und X die in Anspruch 1 angegebenen Bedeutungen haben,
können vorzugsweise erhalten werden, indem man Verbindungen der
Formel IV mit Verbindungen der Formel V umsetzt.

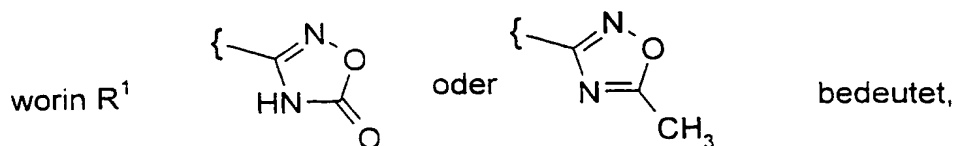
- 20 In den Verbindungen der Formel IV bedeutet L vorzugsweise Cl, Br, I oder
eine reaktionsfähig abgewandelte OH-Gruppe wie z.B. ein aktivierter
Ester, ein Imidazolid oder Alkylsulfonyloxy mit 1-6 C-Atomen (bevorzugt
Methylsulfonyloxy) oder Arylsulfonyloxy mit 6-10 C-Atomen (bevorzugt
Phenyl- oder p-Tolylsulfonyloxy).

- 25 Die Umsetzung der Verbindungen der Formel IV mit Verbindungen der
Formel V erfolgt vorzugsweise in einem inerten Lösungsmittel, unter Zu-
satz einer Base und bei Temperaturen wie oben angegeben.

- 30 Die Ausgangsverbindungen der Formel IV und V sind in der Regel be-
kannt. Sind sie neu, so können aber nach an sich bekannten Methoden
hergestellt werden.

Verbindungen der Formel I,

35



Y CONH bedeutet,

und R^2 und X die in Anspruch 1 angegebenen Bedeutungen haben, können vorzugsweise erhalten werden, indem man Verbindungen der Formel VI mit Verbindungen der Formel V umsetzt.

Die Umsetzung der Verbindungen der Formel VI mit Verbindungen der Formel V erfolgt vorzugsweise in einem inerten Lösungsmittel und bei Temperaturen wie oben angegeben.

Die Ausgangsverbindungen der Formel VI sind in der Regel bekannt. Sind sie neu, so können aber nach an sich bekannten Methoden hergestellt werden.

Verbindungen der Formel I, worin R^1 $-C(=NH)-NH_2$ bedeutet, können ferner aus der entsprechenden Cyanverbindung erhalten werden.

Die Umwandlung einer Cyangruppe in eine Amidinogruppe erfolgt durch Umsetzung mit z.B. Hydroxylamin und anschließender Reduktion des N-Hydroxyamidins mit Wasserstoff in Anwesenheit eines Katalysators wie z.B. Pd/C.

Zur Herstellung eines Amidins der Formel I ($R^1 = -C(=NH)-NH_2$) kann man an ein Nitril der Formel I ($R^1 = CN$) auch Ammoniak anlagern. Die Anlagerung erfolgt bevorzugt mehrstufig, indem man in an sich bekannter Weise a) das Nitril mit H_2S in ein Thioamid umwandelt, das mit einem Alkylierungsmittel, z.B. CH_3I , in den entsprechenden S-Alkyl-imidothioester übergeführt wird, welcher seinerseits mit NH_3 zum Amidin reagiert, b) das Nitril mit einem Alkohol, z.B. Ethanol in Gegenwart von HCl in den entsprechenden Imidoester umwandelt und diesen mit Ammoniak behandelt, oder c) das Nitril mit Lithium-bis-(trimethylsilyl)-amid umsetzt und das Produkt anschließend hydrolysiert.

Es ist ferner möglich, eine Verbindung der Formel I in eine andere Verbindung der Formel I umzuwandeln, indem man einen oder mehrere Rest(e) R^1 , R^2 , R^3 , R^4 und/oder R^5 in einen oder mehrere Rest(e) R^1 , R^2 , R^3 , R^4 und/oder R^5 umwandelt, z.B. indem man Nitrogruppen (beispiels-

weise durch Hydrierung an Raney-Nickel oder Pd-Kohle in einem inerten Lösungsmittel wie Methanol oder Ethanol) zu Aminogruppen reduziert.

5 Ester können z.B. mit Essigsäure oder mit NaOH oder KOH in Wasser, Wasser-THF oder Wasser-Dioxan bei Temperaturen zwischen 0 und 100° verseift werden.

10 Ferner kann man freie Aminogruppen in üblicher Weise mit einem Säurechlorid oder -anhydrid acylieren oder mit einem unsubstituierten oder substituierten Alkylhalogenid alkylieren, zweckmäßig in einem inerten Lösungsmittel wie Dichlormethan oder THF und /oder in Gegenwart einer Base wie Triethylamin oder Pyridin bei Temperaturen zwischen -60 und +30°.

15 Eine Base der Formel I kann mit einer Säure in das zugehörige Säureadditionssalz übergeführt werden, beispielsweise durch Umsetzung äquivalenter Mengen der Base und der Säure in einem inerten Lösungsmittel wie Ethanol und anschließendes Eindampfen. Für diese Umsetzung kommen insbesondere Säuren in Frage, die physiologisch unbedenkliche Salze liefern. So können anorganische Säuren verwendet werden, z.B.

20 Schwefelsäure, Salpetersäure, Halogenwasserstoffsäuren wie Chlorwasserstoffsäure oder Bromwasserstoffsäure, Phosphorsäuren wie Orthophosphorsäure, Sulfaminsäure, ferner organische Säuren, insbesondere aliphatische, alicyclische, araliphatische, aromatische oder heterocyclische

25 ein- oder mehrbasige Carbon-, Sulfon- oder Schwefelsäuren, z.B. Ameisensäure, Essigsäure, Propionsäure, Pivalinsäure, Diethylessigsäure, Malonsäure, Bernsteinsäure, Pimelinsäure, Fumarsäure, Maleinsäure, Milchsäure, Weinsäure, Äpfelsäure, Citronensäure, Gluconsäure, Ascorbinsäure, Nicotinsäure, Isonicotinsäure, Methan- oder Ethansulfonsäure,

30 Ethandisulfonsäure, 2-Hydroxyethansulfonsäure, Benzolsulfonsäure, p-Toluolsulfonsäure, Naphthalin-mono- und disulfonsäuren, Laurylschwefelsäure. Salze mit physiologisch nicht unbedenklichen Säuren, z.B. Pikrate, können zur Isolierung und /oder Aufreinigung der Verbindungen der Formel I verwendet werden.

35

Andererseits können Verbindungen der Formel I mit Basen (z.B. Natrium- oder Kaliumhydroxid oder -carbonat) in die entsprechenden Metall-, insbesondere Alkalimetall- oder Erdalkalimetall-, oder in die entsprechenden Ammoniumsalze umgewandelt werden.

5

Erfindungsgemäße Verbindungen der Formel I können aufgrund ihrer Molekülstruktur chiral sein und können dementsprechend in verschiedenen enantiomeren Formen auftreten. Sie können daher in racemischer oder in optisch aktiver Form vorliegen.

10

Da sich die pharmazeutische Wirksamkeit der Racemate bzw. der Stereoisomeren der erfindungsgemäßen Verbindungen unterscheiden kann, kann es wünschenswert sein, die Enantiomere zu verwenden. In diesen Fällen kann das Endprodukt oder aber bereits die Zwischenprodukte in enantiomere Verbindungen, durch dem Fachmann bekannte chemische oder physikalische Maßnahmen, aufgetrennt oder bereits als solche bei der Synthese eingesetzt werden.

15

20

Im Falle racemischer Amine werden aus dem Gemisch durch Umsetzung mit einem optisch aktiven Trennmittel Diastereomere gebildet. Als Trennmittel eignen sich z.B. optisch aktiven Säuren, wie die R- und S-Formen von Weinsäure, Diacetylweinsäure, Dibenzoylweinsäure, Mandelsäure, Äpfelsäure, Milchsäure, geeignet N-geschützte Aminosäuren (z.B. N-Benzoylprolin oder N-Benzolsulfonylprolin) oder die verschiedenen optisch aktiven Camphersulfonsäuren. Vorteilhaft ist auch eine chromatographische Enantiomerentrennung mit Hilfe eines optisch aktiven Trennmittels (z.B. Dinitrobenzoylphenylglycin, Cellulosetriacetat oder andere Derivate von Kohlenhydraten oder auf Kieselgel fixierte chiral derivatisierte Methacrylatpolymere). Als Laufmittel eignen sich hierfür wäßrige oder alkoholische Lösungsmittelgemische wie z.B. Hexan/Isopropanol/ Acetonitril z.B. im Verhältnis 82:15:3.

25

30

35

Gegenstand der Erfindung ist ferner die Verwendung der Verbindungen der Formel I und/oder ihrer physiologisch unbedenklichen Salze zur Herstellung pharmazeutischer Zubereitungen, insbesondere auf nicht-chemischem Wege. Hierbei können sie zusammen mit mindestens einem festen, flüssigen und/oder halbflüssigen Träger- oder Hilfsstoff und gege-

benenfalls in Kombination mit einem oder mehreren weiteren Wirkstoffen in eine geeignete Dosierungsform gebracht werden.

5 Gegenstand der Erfindung sind ferner pharmazeutische Zubereitungen, enthaltend mindestens eine Verbindung der Formel I und/oder eines ihrer physiologisch unbedenklichen Salze.

10 Diese Zubereitungen können als Arzneimittel in der Human- oder Veterinärmedizin verwendet werden. Als Trägerstoffe kommen organische oder anorganische Substanzen in Frage, die sich für die enterale (z.B. orale), parenterale oder topische Applikation eignen und mit den neuen Verbindungen nicht reagieren, beispielsweise Wasser, pflanzliche Öle, Benzylalkohole, Alkylenglykole, Polyethylenglykole, Glycerintriacetat, Gelatine, Kohlehydrate wie Lactose oder Stärke, Magnesiumstearat, Talk, Vaseline.

15 Zur oralen Anwendung dienen insbesondere Tabletten, Pillen, Dragees, Kapseln, Pulver, Granulate, Sirupe, Säfte oder Tropfen, zur rektalen Anwendung Suppositorien, zur parenteralen Anwendung Lösungen, vorzugsweise ölige oder wässrige Lösungen, ferner Suspensionen, Emulsionen oder Implantate, für die topische Anwendung Salben, Cremes oder Puder.

20 Die neuen Verbindungen können auch lyophilisiert und die erhaltenen Lyophilisate z.B. zur Herstellung von Injektionspräparaten verwendet werden. Die angegebenen Zubereitungen können sterilisiert sein und/oder Hilfsstoffe wie Gleit-, Konservierungs-, Stabilisierungs- und/oder Netzmittel, Emulgatoren, Salze zur Beeinflussung des osmotischen Druckes, Puffersubstanzen, Farb-, Geschmacks- und /oder mehrere weitere Wirkstoffe enthalten, z.B. ein oder mehrere Vitamine.

25

30 Die Verbindungen der Formel I und ihre physiologisch unbedenklichen Salze können bei der Bekämpfung und Verhütung von thromboembolischen Erkrankungen wie Thrombose, myocardialen Infarkt, Arteriosklerose, Entzündungen, Apoplexie, Angina pectoris, Restenose nach Angioplastie und Claudicatio intermittens verwendet werden.

35 Dabei werden die erfindungsgemäßen Substanzen in der Regel vorzugsweise in Dosierungen zwischen etwa 1 und 500 mg, insbesondere zwischen 5 und 100 mg pro Dosierungseinheit verabreicht. Die tägliche Do-

- sierung liegt vorzugsweise zwischen etwa 0,02 und 10 mg/kg Körpergewicht. Die spezielle Dosis für jeden Patienten hängt jedoch von den verschiedensten Faktoren ab, beispielsweise von der Wirksamkeit der eingesetzten speziellen Verbindung, vom Alter, Körpergewicht, allgemeinen Gesundheitszustand, Geschlecht, von der Kost, vom Verabreichungszeitpunkt und -weg, von der Ausscheidungsgeschwindigkeit, Arzneistoffkombination und Schwere der jeweiligen Erkrankung, welcher die Therapie gilt. Die orale Applikation ist bevorzugt.
- 10 Vor- und nachstehend sind alle Temperaturen in °C angegeben. In den nachfolgenden Beispielen bedeutet "übliche Aufarbeitung": Man gibt, falls erforderlich, Wasser hinzu, stellt, falls erforderlich, je nach Konstitution des Endprodukts auf pH-Werte zwischen 2 und 10 ein, extrahiert mit Ethylacetat oder Dichlormethan, trennt ab, trocknet die organische Phase über Natriumsulfat, dampft ein und reinigt durch Chromatographie an Kieselgel
- 15 und /oder durch Kristallisation. Rf-Werte an Kieselgel; Laufmittel: Ethylacetat/Methanol 9:1.
- Massenspektrometrie (MS): EI (Elektronenstoß-Ionisation) M^+
FAB (Fast Atom Bombardment) $(M+H)^+$
- 20 Beispiel 1
- Zu einer Lösung von 10,0 g 4-(5-Methyl-1,2,4-oxadiazol-3-yl)-benzoesäure in 150 ml Toluol gibt man 46 ml Thionylchlorid und 1 ml DMF. Die Lösung wird 5 Stunden unter Rückfluß erhitzt. Nach Entfernen des Lösungsmittels
- 25 erhält man 4-(5-Methyl-1,2,4-oxadiazol-3-yl)-benzoylchlorid, EI 222.
- Durch anschließende Umsetzung mit 9,3 g 1-tert.-Butoxycarbonylpiperazin in 150 ml Dichlormethan und 48 ml Triethylamin erhält nach üblicher Aufarbeitung 4-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-benzoyl]-piperazin-1-carbonsäure-tert.-butylester, FAB 373.
- 30 Die Abspaltung der BOC-Gruppe erfolgt mit 4N HCl in Dioxan.
- Eine Lösung von 100 mg des erhaltenen [4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-piperazin-1-yl-methanon ("A") und 120 mg 6-Chlornaphthalin-2-sulfonylchlorid in 5 ml Dichlormethan wird mit 400 mg 4-Dimethylaminopyridin auf Polystyrol versetzt und 18 Stunden bei Raumtemperatur nach-
- 35 gerührt. Nach Filtration und Entfernen des Lösungsmittels erhält man [4-

(6-Chlornaphthalin-2-sulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon, FAB 497.

Analog erhält man durch Umsetzung von "A"

5

mit 4-Biphenyl-2-sulfonylchlorid

[4-(4-Biphenylsulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;

10

mit 2-Naphthyl-sulfonylchlorid

[4-(2-Naphthyl-sulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;

mit 4-Propylphenyl-sulfonylchlorid

15

[4-(4-Propylphenyl-sulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;

mit 2-Phenylvinyl-sulfonylchlorid

20

[4-(2-Phenylvinyl-sulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;

mit 3-Nitro-4-chlorphenyl-sulfonylchlorid

[4-(3-Nitro-4-chlorphenyl-sulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;

25

mit 2-Nitro-4-methoxyphenyl-sulfonylchlorid

[4-(2-Nitro-4-methoxyphenyl-sulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;

30

mit p-Tolyl-sulfonylchlorid

[4-(4-Tolylsulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;

mit Decylsulfonylchlorid

35

[4-(Decylsulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;

- mit Benzylsulfonylchlorid
[4-(Benzylsulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;
5
- mit 3-Nitro-6-methylbenzyl-sulfonylchlorid
[4-(3-Nitro-6-methylbenzyl-sulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;
- 10 mit 2,3-Dichlorphenyl-sulfonylchlorid
[4-(2,3-Dichlorphenyl-sulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;
- mit 3,4-Dichlorphenyl-sulfonylchlorid
15 [4-(3,4-Dichlorphenyl-sulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;
- mit Phenylsulfonylchlorid
[4-(Phenylsulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;
20
- mit 3-Bromphenyl-sulfonylchlorid
[4-(3-Bromphenyl-sulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;
25
- mit 3,4-Dimethoxyphenyl-sulfonylchlorid
[4-(3,4-Dimethoxyphenyl-sulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;
- 30 mit 4-Acetamido-3-chlorphenyl-sulfonylchlorid
[4-(4-Acetamido-3-chlorphenyl-sulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;
- mit 4-Chlor-2,5-dimethylphenyl-sulfonylchlorid
35 [4-(4-Chlor-2,5-dimethylphenyl-sulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;

mit m-Tolyl-sulfonylchlorid

[4-(3-Tolylsulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;

5

mit 2-Methoxy-5-methylphenyl-sulfonylchlorid

[4-(2-Methoxy-5-methylphenyl-sulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;

10

mit 3-Chlorphenyl-sulfonylchlorid

[4-(3-Chlorphenyl-sulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;

mit 4-Methoxyphenyl-sulfonylchlorid

15

[4-(4-Methoxyphenyl-sulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;

mit 2-Thienyl-sulfonylchlorid

20

[4-(2-Thienyl-sulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;

mit 4-Chlorphenyl-sulfonylchlorid

[4-(4-Chlorphenyl-sulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;

25

mit Isopropylsulfonylchlorid

[4-(Isopropylsulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;

30

mit 8-Chinolylsulfonylchlorid

[4-(8-Chinolylsulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;

mit 4-Nitro-phenyl-sulfonylchlorid

35

[4-(4-Nitrophenyl-sulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;

- mit 3-Chlor-6-methoxyphenyl-sulfonylchlorid
[4-(3-Chlor-6-methoxyphenyl-sulfonyl)-piperazin-1-yl]-[4-(5-methyl-
[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;
5
- mit 4-Acetamidophenyl-sulfonylchlorid
[4-(4-Acetamidophenyl-sulfonyl)-piperazin-1-yl]-[4-(5-methyl-
[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;
- 10 mit 2,2,5,7,8-Pentamethylchroman-6-yl-sulfonylchlorid
[4-(2,2,5,7,8-Pentamethylchroman-6-yl-sulfonyl)-piperazin-1-yl]-[4-(5-
methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;
- mit Campher-10-yl-sulfonylchlorid
15 [4-(Campher-10-yl-sulfonyl)-piperazin-1-yl]-[4-(5-methyl-
[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;
- mit 5-(1-Methyl-5-trifluormethyl-3-pyrazolyl)-2-thienyl-sulfonylchlorid
[4-[5-(1-Methyl-5-trifluormethyl-3-pyrazolyl)-2-thienylsulfonyl]-
20 piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;
- mit 2,5-Dichlorphenyl-sulfonylchlorid
[4-(2,5-Dichlorphenyl-sulfonyl)-piperazin-1-yl]-[4-(5-methyl-
[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;
25
- mit 2,4,6-Trimethylphenyl-sulfonylchlorid
[4-(2,4,6-Trimethylphenyl-sulfonyl)-piperazin-1-yl]-[4-(5-methyl-
[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;
- 30 mit 2-Methylsulfonylphenyl-sulfonylchlorid
[4-(2-Methylsulfonylphenyl-sulfonyl)-piperazin-1-yl]-[4-(5-methyl-
[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;
- mit 5-Benzamidomethyl-2-thienyl-sulfonylchlorid
35 [4-(5-Benzamidomethyl-2-thienyl-sulfonyl)-piperazin-1-yl]-[4-(5-
methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;

- mit Methylsulfonylchlorid
[4-(Methylsulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;
5
- mit 1,3-Dimethyl-5-chlor-4-pyrazolyl-sulfonylchlorid
[4-(1,3-Dimethyl-5-chlor-4-pyrazolyl-sulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;
- 10 mit 3,5-Dimethyl-4-isoxazolyl-sulfonylchlorid
[4-(3,5-Dimethyl-4-isoxazolyl-sulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;
- mit 4-Brom-2-ethylphenyl-sulfonylchlorid
15 [4-(4-Brom-2-ethylphenyl-sulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;
- mit 1-Naphthylsulfonylchlorid
[4-(1-Naphthylsulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;
20
- mit 5-Dimethylamino-1-naphthylsulfonylchlorid
[4-(5-Dimethylamino-1-naphthylsulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;
25
- mit 3,4-Difluorphenyl-sulfonylchlorid
[4-(3,4-Difluorphenyl-sulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;
- 30 mit 4-tert.-Butylphenyl-sulfonylchlorid
[4-(4-tert.-Butylphenyl-sulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;
- mit 4-Ethylphenyl-sulfonylchlorid
35 [4-(4-Ethylphenyl-sulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;

mit 4-(1,1-Dimethylpropyl)-phenyl-sulfonylchlorid

[4-(4-(1,1-Dimethylpropyl)-phenyl-sulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;

5

mit 4-Isopropylphenyl-sulfonylchlorid

[4-(4-Isopropylphenyl-sulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;

10

mit 4-Trifluormethylphenyl-sulfonylchlorid

[4-(4-Trifluormethylphenyl-sulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;

mit 3-Nitro-4-methylphenyl-sulfonylchlorid

15

[4-(3-Nitro-4-methylphenyl-sulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;

mit 4-Pentylphenyl-sulfonylchlorid

20

[4-(4-Pentylphenyl-sulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;

mit 4-Butylphenyl-sulfonylchlorid

[4-(4-Butylphenyl-sulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;

25

mit 3-Chlor-4-methylphenyl-sulfonylchlorid

[4-(3-Chlor-4-methylphenyl-sulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;

30

Beispiel 2

Eine Lösung von 100 mg [4-(6-Chlornaphthalin-2-sulfonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon in 5 ml Methanol wird mit 100 mg Raney-Nickel und einem Tropfen Essigsäure versetzt und bis zum Stillstand bei Normaldruck und Raumtemperatur hydriert. Nach Ent-

35

fernen des Katalysators und des Lösungsmittels erhält man 4-[4-(6-Chlor-naphthalin-2-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 457.

5 Analog erhält man aus den unter Beispiel 1 aufgeführten Methanonderiva-
ten die nachstehenden Verbindungen

- 4-[4-(4-Biphenylsulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 449;
- 10 4-[4-(2-Naphthylsulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, EI 405 ($M^+ - NH_2$);
- 4-[4-(4-Propylphenylsulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 415;
- 4-[4-(2-Phenylvinylsulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 399;
- 15 4-[4-(3-Amino-4-chlorphenylsulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 422;
- 4-[4-(2-Amino-4-methoxyphenylsulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 418;
- 20 4-[4-(4-Tolylsulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 387;
- 4-[4-(Decylsulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 437;
- 4-[4-(Benzylsulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 387;
- 25 4-[4-(3-Amino-6-methylbenzylsulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 402;
- 4-[4-(2,3-Dichlorphenyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 441;
- 4-[4-(3,4-Dichlorphenyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 441;
- 30 4-[4-(Phenyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 373;
- 4-[4-(3-Bromphenyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 451,453;
- 35 4-[4-(3,4-Dimethoxyphenyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 433;

- 4-[4-(4-Acetamido-3-chlorophenyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 464;
- 4-[4-(4-Chlor-2,5-dimethylphenyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 435;
- 5 4-[4-(3-Tolylsulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 387;
- 4-[4-(2-Methoxy-5-methylphenyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 417;
- 10 4-[4-(3-Chlorophenyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 407;
- 4-[4-(4-Methoxyphenyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 402;
- 4-[4-(2-Thienyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 379;
- 15 4-[4-(4-Chlorophenyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 407;
- 4-[4-(Isopropylsulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 339;
- 20 4-[4-(1,2,3,4-Tetrahydrochinolin-8-yl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 428;
- 4-[4-(4-Aminophenyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 388;
- 4-[4-(3-Chlor-6-methoxyphenyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 437;
- 25 4-[4-(4-Acetamidophenyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 437;
- 4-[4-(2,2,5,7,8-Pentamethylchroman-6-yl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 499;
- 4-[4-(Campher-10-yl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 447;
- 30 4-[4-[5-(1-Methyl-5-trifluormethyl-3-pyrazolyl)-2-thienyl-sulfonyl]-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 527;
- 4-[4-(2,5-Dichlorophenyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 441;
- 35 4-[4-(2,4,6-Trimethylphenyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 415;

- 4-[4-(2-Methylsulfonylphenyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 451;
- 4-[4-(5-Benzamidomethyl-2-thienyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 512;
- 5 4-[4-(Methylsulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, EI 292 ($M^+ - NH_2$);
- 4-[4-(1,3-Dimethyl-5-chlor-4-pyrazolyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat;
- 10 4-[4-(3,5-Dimethyl-4-isoxazolyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat;
- 4-[4-(4-Brom-2-ethylphenyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, EI 461, 463 ($M^+ - NH_2$);
- 4-[4-(1-Naphthylsulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, EI 405 ($M^+ - NH_2$);
- 15 4-[4-(5-Dimethylamino-1-naphthylsulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, EI 448 ($M^+ - NH_2$);
- 4-[4-(3,4-Difluorphenyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat;
- 4-[4-(4-tert.-Butylphenyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 429;
- 20 4-[4-(4-Ethylphenyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 401;
- 4-[4-(4-(1,1-Dimethylpropyl)-phenyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 442;
- 25 4-[4-(4-Isopropylphenyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 415;
- 4-[4-(4-Trifluormethylphenyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 441;
- 4-[4-(3-Amino-4-methylphenyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 402;
- 30 4-[4-(4-Pentylphenyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 443;
- 4-[4-(4-Butylphenyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 429;
- 35 4-[4-(3-Chlor-4-methylphenyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 421.

Beispiel 3

5 Durch Umsetzung mit äquimolaren Mengen Chlorameisensäuremethylester in Pyridin und katalytischen Mengen Dimethylaminopyridin erhält man
aus 4-[4-(6-Chlornaphthalin-2-sulfonyl)-piperazin-1-carbonyl]-benzamidin
nach üblicher Aufarbeitung die Verbindung {Imino-[4-(4-(6-Chlornaphthalin-2-sulfonyl)-piperazin-1-carbonyl)-phenyl]-methyl}-carbaminsäure-
10 methylester.

Beispiel 4

15 Analog Beispiel 1 erhält man durch Umsetzung von 3-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-1-piperazin-1-yl-propan-1-on [erhältlich aus 3-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-1-(4-tert.-butyl-oxy-carbonyl)-piperazin-1-yl-propan-1-on durch Behandlung mit TFA/CH₂Cl₂] und 6-Chlornaphthalin-2-sulfonylchlorid die Verbindung 1-[4-(6-Chlornaphthalin-2-sulfonyl)-piperazin-1-yl]-3-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-
20 propan-1-on und nach Hydrierung 4-{3-Oxo-3-[4-(6-chlornaphthalin-2-sulfonyl)-piperazin-1yl]-propyl}-benzamidin.

Beispiel 5

25 Analog Beispiel 1 und 2 erhält man durch Umsetzung von [3-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-piperazin-1-yl-methanon und 5-Chlornaphthalin-2-sulfonylchlorid und anschließender Hydrierung die Verbindung 3-[4-(6-Chlornaphthalin-2-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 457.

30

Analog erhält man durch Umsetzung von [3-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-piperazin-1-yl-methanon mit 4-Propylphenyl-sulfonylchlorid und anschließender Hydrierung die Verbindung 3-[4-(4-Propylphenyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 415.

35

Beispiel 6

5 Analog Beispiel 1 erhält man durch Umsetzung von 2-[4-(5-Methyl-
[1,2,4]oxadiazol-3-yl)-phenyl]-1-piperazin-1-yl-ethan-1-on ("B") und 4-
Propylphenyl-sulfonylchlorid die Verbindung 1-[4-(4-Propylphenylsulfonyl)-
piperazin-1-yl]-2-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-ethan-1-on und
nach Hydrierung 4-{2-Oxo-2-[4-(4-propylphenylsulfonyl)-piperazin-1yl]-
ethyl}-benzamidin, FAB 429.

10

Analog erhält man durch Umsetzung von "B"

mit Decylsulfonylchlorid

15

1-[4-(Decylsulfonyl)-piperazin-1-yl]-2-[4-(5-methyl-[1,2,4]oxadiazol-3-
yl)-phenyl]-ethan-1-on;

mit Phenylsulfonylchlorid

20

1-[4-(Phenylsulfonyl)-piperazin-1-yl]-2-[4-(5-methyl-[1,2,4]oxadiazol-3-
yl)-phenyl]-ethan-1-on;

mit 3,4-Dichlorphenyl-sulfonylchlorid

1-[4-(3,4-Dichlorphenyl-sulfonyl)-piperazin-1-yl]-2-[4-(5-methyl-
[1,2,4]oxadiazol-3-yl)-phenyl]-ethan-1-on;

25

mit Benzylsulfonylchlorid

1-[4-(Benzylsulfonyl)-piperazin-1-yl]-2-[4-(5-methyl-[1,2,4]oxadiazol-3-
yl)-phenyl]-ethan-1-on;

mit 3,4-Dimethoxyphenyl-sulfonylchlorid

30

1-[4-(3,4-Dimethoxyphenyl-sulfonyl)-piperazin-1-yl]-2-[4-(5-methyl-
[1,2,4]oxadiazol-3-yl)-phenyl]-ethan-1-on;

mit Isopropylsulfonylchlorid

35

1-[4-(Isopropyl-sulfonyl)-piperazin-1-yl]-2-[4-(5-methyl-
[1,2,4]oxadiazol-3-yl)-phenyl]-ethan-1-on;

- mit Campher-10-yl-sulfonylchlorid
1-[4-(Campher-10-yl-sulfonyl)-piperazin-1-yl]-2-[4-(5-methyl-
[1,2,4]oxadiazol-3-yl)-phenyl]-ethan-1-on;
- 5 mit 3-Methoxy-4-methoxycarbonyl-2-thienyl-sulfonylchlorid
1-[4-(3-Methoxy-4-methoxycarbonyl-2-thienyl-sulfonyl)-piperazin-1-yl]-
2-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-ethan-1-on;
- mit 2,4,6-Trimethylphenyl-sulfonylchlorid
10 1-[4-(2,4,6-Trimethylphenyl-sulfonyl)-piperazin-1-yl]-2-[4-(5-methyl-
[1,2,4]oxadiazol-3-yl)-phenyl]-ethan-1-on;
- mit 2-Phenylvinyl-sulfonylchlorid
15 1-[4-(2-Phenylvinyl-sulfonyl)-piperazin-1-yl]-2-[4-(5-methyl-
[1,2,4]oxadiazol-3-yl)-phenyl]-ethan-1-on;
- mit Methylsulfonylchlorid
20 1-[4-(Methylsulfonyl)-piperazin-1-yl]-2-[4-(5-methyl-[1,2,4]oxadiazol-3-
yl)-phenyl]-ethan-1-on;
- mit [2,1,3]-Benzothiadiazol-4-yl-sulfonylchlorid
1-[4-([2,1,3]-Benzothiadiazol-4-yl-sulfonyl)-piperazin-1-yl]-2-[4-(5-
methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-ethan-1-on;
- 25 mit 2,4-Dichlorphenyl-sulfonylchlorid
1-[4-(2,4-Dichlorphenyl-sulfonyl)-piperazin-1-yl]-2-[4-(5-methyl-
[1,2,4]oxadiazol-3-yl)-phenyl]-ethan-1-on;
- mit 1-Naphthyl-sulfonylchlorid
30 1-[4-(1-Naphthyl-sulfonyl)-piperazin-1-yl]-2-[4-(5-methyl-
[1,2,4]oxadiazol-3-yl)-phenyl]-ethan-1-on;
- mit 2-Naphthyl-sulfonylchlorid
35 1-[4-(2-Naphthyl-sulfonyl)-piperazin-1-yl]-2-[4-(5-methyl-
[1,2,4]oxadiazol-3-yl)-phenyl]-ethan-1-on;

mit 5-Dimethylamino-1-naphthyl-sulfonylchlorid

1-[4-(5-Dimethylamino-1-naphthyl-sulfonyl)-piperazin-1-yl]-2-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-ethan-1-on;

5 mit 4-Methylsulfonylphenyl-sulfonylchlorid

1-[4-(4-Methylsulfonylphenyl-sulfonyl)-piperazin-1-yl]-2-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-ethan-1-on.

Durch Hydrierung erhält man daraus nachstehende Amidinderivate

10

4-{2-Oxo-2-[4-(decylsulfonyl)-piperazin-1yl]-ethyl}-benzamidin, Acetat, FAB 450;

4-{2-Oxo-2-[4-(phenylsulfonyl)-piperazin-1yl]-ethyl}-benzamidin, Acetat, FAB 387;

15

4-{2-Oxo-2-[4-(3,4-dichlorphenyl-sulfonyl)-piperazin-1yl]-ethyl}-benzamidin, Acetat, FAB 454;

4-{2-Oxo-2-[4-(benzylsulfonyl)-piperazin-1yl]-ethyl}-benzamidin, Acetat, FAB 401;

20

4-{2-Oxo-2-[4-(3,4-dimethoxyphenyl-sulfonyl)-piperazin-1yl]-ethyl}-benzamidin, Acetat, FAB 447;

4-{2-Oxo-2-[4-(isopropyl-sulfonyl)-piperazin-1yl]-ethyl}-benzamidin, Acetat, FAB 353;

4-{2-Oxo-2-[4-(campher-10-yl-sulfonyl)-piperazin-1yl]-ethyl}-benzamidin, Acetat, FAB 353;

25

4-{2-Oxo-2-[4-(3-methoxy-4-methoxycarbonyl-2-thienyl-sulfonyl)-piperazin-1yl]-ethyl}-benzamidin, Acetat, FAB 481;

4-{2-Oxo-2-[4-(2,4,6-trimethylphenyl-sulfonyl)-piperazin-1yl]-ethyl}-benzamidin, Acetat, FAB 429;

30

4-{2-Oxo-2-[4-(2-Phenylvinyl-sulfonyl)-piperazin-1yl]-ethyl}-benzamidin, Acetat, FAB 413;

4-{2-Oxo-2-[4-(methylsulfonyl)-piperazin-1yl]-ethyl}-benzamidin, Acetat, FAB 325;

4-{2-Oxo-2-[4-(2,3-diaminophenylsulfonyl)-piperazin-1yl]-ethyl}-benzamidin, Acetat, FAB 415;

35

4-{2-Oxo-2-[4-(2,4-dichlorphenylsulfonyl)-piperazin-1yl]-ethyl}-benzamidin, Acetat, FAB 455;

4-{2-Oxo-2-[4-(1-naphthyl-sulfonyl)-piperazin-1-yl]-ethyl}-benzamidin,
Acetat, FAB 437;

4-{2-Oxo-2-[4-(2-naphthyl-sulfonyl)-piperazin-1-yl]-ethyl}-benzamidin,
Acetat, FAB 437;

5 4-{2-Oxo-2-[4-(5-dimethylamino-1-naphthyl-sulfonyl)-piperazin-1-yl]-
ethyl}-benzamidin, Acetat, FAB 480;

4-{2-Oxo-2-[4-(4-methylsulfonylphenyl-sulfonyl)-piperazin-1-yl]-ethyl}-
benzamidin, Acetat, FAB 465.

10 Beispiel 7

Analog Beispiel 1 erhält man durch Umsetzung von "A"

mit 4-Biphenylyl-carbonsäurechlorid

15 [4-(4-Phenyl-benzoyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-
yl)-phenyl]-methanon;

mit Cyclopentyl-carbonsäurechlorid

20 [4-(Cyclopentylcarbonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-
3-yl)-phenyl]-methanon;

mit Phenoxy-acetylchlorid

25 [4-(Phenoxyacetyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-
phenyl]-methanon;

mit 1-Naphthyl-carbonsäurechlorid

[4-(1-Naphthylcarbonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-
3-yl)-phenyl]-methanon;

30 mit 2-Naphthyl-carbonsäurechlorid

[4-(2-Naphthylcarbonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-
3-yl)-phenyl]-methanon;

mit Nicotinoylchlorid

35 [4-(Nicotinoyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-
phenyl]-methanon;

mit 3-Nitro-benzoylchlorid

[4-(3-Nitro-benzoyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;

5

mit Benzo-[b]thiophen-2-carbonsäurechlorid

[4-(Benzo-[b]thiophen-2-carbonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;

10

mit 4-Trifluormethoxy-benzoylchlorid

[4-(4-Trifluormethoxy-benzoyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;

mit 2,5-Dimethoxyphenyl-acetylchlorid

15

[4-(2,5-Dimethoxyphenyl-acetyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;

mit 4-Chlorphenyl-acetylchlorid

20

[4-(4-Chlorphenyl-acetyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;

mit 1,3-Benzodioxol-5-carbonsäurechlorid

[4-(1,3-Benzodioxol-5-carbonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;

25

mit 3,4-Dichlorbenzoylchlorid

[4-(3,4-Dichlorbenzoyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon;

30

mit Chlorameisensäureisobutylester

[4-(Isobutyloxycarbonyl)-piperazin-1-yl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanon.

Durch Hydrierung erhält man daraus nachstehende Amidinderivate

35

- 4-[4-(4-Phenyl-benzoyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 413;
- 4-[4-(Cyclopentylcarbonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 329;
- 5 4-[4-(Phenoxyacetyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 367;
- 4-[4-(1-Naphthylcarbonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 387;
- 10 4-[4-(2-Naphthylcarbonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 387;
- 4-[4-(Nicotinoyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 338;
- 4-[4-(3-Aminobenzoyl)-piperazin-1-carbonyl]-benzamidin;
- 4-[4-(Benzo-[b]thiophen-2-carbonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 393;
- 15 4-[4-(4-Trifluormethoxy-benzoyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 421;
- 4-[4-(2,5-Dimethoxyphenyl-acetyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 411;
- 4-[4-(4-Chlorphenyl-acetyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 385;
- 20 4-[4-(1,3-Benzodioxol-5-carbonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 381;
- 4-[4-(3,4-Dichlorbenzoyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 381;
- 25 4-[4-(Isobutyloxy-carbonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 333.

Beispiel 8

- 30 Durch Umsetzung mit äquimolaren Mengen Acetylchlorid in Pyridin und katalytischer Mengen Dimethylaminopyridin erhält man nach üblicher Aufarbeitung
- aus 4-[4-(6-Chlornaphthalin-2-sulfonyl)-piperazin-1-carbonyl]-benzamidin
- 35 N-{Imino-4-[4-(6-Chlornaphthalin-2-sulfonyl)-piperazin-1-carbonyl]-phenyl-methyl}-acetamid.

Beispiel 9

5 Durch Umsetzung äquimolarer Mengen 4-Cyanbenzylbromid, BOC-Piperazin und Triethylamin in Dichlormethan erhält man 1-(4-Cyan-benzyl)-4-(tert.-butyloxycarbonyl)-piperazin. Durch Umsetzung mit
a) Hydroxylaminhydrochlorid, Triethylamin in Ethanol und
b) Acetanhydrid
erhält man 1-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-benzyl]-4-(tert.-
10 butyloxycarbonyl)-piperazin.

Nach Abspaltung der BOC-Gruppe mit TFA in CH₂Cl₂ erhält man analog
Beispiel 1 und 2 durch Umsetzung von 1-[4-(5-Methyl-[1,2,4]oxadiazol-3-
yl)-benzyl]-piperazin mit 6-Chlornaphthalin-2-sulfonylchlorid, anschließen-
15 der Hydrierung und üblicher Aufarbeitung die Verbindung 4-[(6-Chlornaphthalin-2-sulfonyl)-piperazin-1-ylmethyl]-benzamidin.

Analog erhält man die nachstehenden Verbindungen

20 4-[(4-Biphenyl-yl-sulfonyl)-piperazin-1-ylmethyl]-benzamidin,
4-[(2-Naphthyl-sulfonyl)-piperazin-1-ylmethyl]-benzamidin,
4-[(4-Propylphenyl-sulfonyl)-piperazin-1-ylmethyl]-benzamidin und
4-[(2-Phenylvinyl-sulfonyl)-piperazin-1-ylmethyl]-benzamidin.

25 Beispiel 10

Durch Umsetzung von äquimolaren Mengen 4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-benzoesäure, Phosphorsäurediphenylesterazid und Triethylamin in DMF erhält man nach üblicher Aufarbeitung 4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-benzoylazid.
30

Durch Erhitzen mit BOC-Piperazin in Toluol erhält man in einer Umlagerungsreaktion nach üblicher Aufarbeitung 1-BOC-4-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenylcarbamoyl]-piperazin. Durch Abspaltung der BOC-Gruppe mit TFA in CH₂Cl₂ erhält man 4-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenylcarbamoyl]-piperazin ("C").
35

Durch Umsetzung von "C" mit 6-Chlornaphthalin-sulfonylchlorid und anschließender Hydrierung erhält man analog Beispiel 1 und 2 die Verbindung 4-(6-Chlornaphthalin-2-sulfonyl)-piperazin-1-carbonsäure-N-(4-amidino-phenyl)-amid.

5

Analog erhält man die nachstehenden Verbindungen

4-(4-Biphenylsulfonyl)-piperazin-1-carbonsäure-N-(4-amidino-phenyl)-amid,

10

4-(2-Naphthyl-sulfonyl)-piperazin-1-carbonsäure-N-(4-amidino-phenyl)-amid,

4-(4-Propylphenyl-sulfonyl)-piperazin-1-carbonsäure-N-(4-amidino-phenyl)-amid und

15

4-(2-Phenylvinyl-sulfonyl)-piperazin-1-carbonsäure-N-(4-amidino-phenyl)-amid.

Beispiel 11

20

Durch Umsetzung äquimolarer Mengen 1-BOC-4-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenylcarbamoyl]-piperazin, Bromessigsäuremethylester und Kalium-tert.butylat in DMF erhält man nach üblicher Aufarbeitung die Verbindung {(4-BOC-piperazin-1-carbonyl)-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-amino}-essigsäuremethylester.

Durch Reaktion mit

25

a) HCl/Dioxan und b) NaOH erhält man die Verbindung {(Piperazin-1-carbonyl)-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-amino}-essigsäuremethylester.

Durch Umsetzung mit 6-Chlornaphthalin-sulfonylchlorid erhält man analog Beispiel 1 die Verbindung {[4-(6-Chlornaphthalin-2-sulfonyl)-piperazin-1-carbonyl]-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-amino}-essigsäuremethylester.

30

Durch Hydrierung an Raney-Nickel erhält man daraus {[4-(6-Chlornaphthalin-2-sulfonyl)-piperazin-1-carbonyl]-[4-amidinophenyl]-amino}-essigsäuremethylester.

35

Die Spaltung des Methylesters erfolgt durch Behandlung mit NaOH in Methanol/Wasser. Nach üblicher Aufarbeitung erhält man die {[4-(6-

Chlornaphthalin-2-sulfonyl)-piperazin-1-carbonyl]-[4-amidinophenyl]-amino}-essigsäure.

Analog erhält man nachstehender Verbindungen

5

{[4-(4-Biphenyl-yl-sulfonyl)-piperazin-1-carbonyl]-[4-amidinophenyl]-amino}-essigsäure,

{[4-(2-Naphthyl-sulfonyl)-piperazin-1-carbonyl]-[4-amidinophenyl]-amino}-essigsäure,

10

{[4-(4-Propylphenyl-sulfonyl)-piperazin-1-carbonyl]-[4-amidinophenyl]-amino}-essigsäure und

{[4-(2-phenylvinyl-sulfonyl)-piperazin-1-carbonyl]-[4-amidinophenyl]-amino}-essigsäure.

15

Beispiel 12

Durch Umsetzung äquimolarer Mengen 4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenylessigsäure, Methyljodid und Kaliumcarbonat erhält man 4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenylessigsäuremethylester ("D").

20

Durch Erhitzen äquimolarer Mengen von BOC-Piperazin und Chloracetylchlorid in Toluol erhält man nach üblicher Aufarbeitung 1-BOC-4-Chlormethylcarbonyl-piperazin ("E").

Durch Umsetzung von "D" und "E" mit NaH in DMF erhält man nach üblicher Aufarbeitung die Verbindung 4-(4-BOC-piperazin-1-yl)-2-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-4-oxo-buttersäuremethylester.

25

Durch Reaktion mit

a) HCl/Dioxan und b) NaOH erhält man die Verbindung 4-(Piperazin-1-yl)-2-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-4-oxo-buttersäuremethylester.

Durch Umsetzung mit 6-Chlornaphthalin-sulfonylchlorid erhält man analog Beispiel 1 die Verbindung 4-[4-(6-Chlornaphthalin-2-sulfonyl)-piperazin-1-yl]-2-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-4-oxo-buttersäuremethylester.

30

Durch Hydrierung analog Beispiel 2 erhält man daraus die Verbindung 4-[4-(6-Chlornaphthalin-2-sulfonyl)-piperazin-1-yl]-2-(4-amidinophenyl)-4-oxo-buttersäuremethylester.

35

Die Spaltung des Methylesters erfolgt durch Behandlung mit NaOH in Methanol/Wasser. Nach üblicher Aufarbeitung erhält man 4-[4-(6-Chlornaphthalin-2-sulfonyl)-piperazin-1-yl]-2-(4-amidinophenyl)-4-oxo-buttersäure.

5

Analog erhält man nachstehende Verbindungen

4-[4-(4-Biphenyl-yl)-sulfonyl]-piperazin-1-yl]-2-(4-amidinophenyl)-4-oxo-buttersäure,

10

4-[4-(2-Naphthyl-sulfonyl)-piperazin-1-yl]-2-(4-amidinophenyl)-4-oxo-buttersäure,

4-[4-(4-Propylphenyl-sulfonyl)-piperazin-1-yl]-2-(4-amidinophenyl)-4-oxo-buttersäure und

15

4-[4-(2-Phenylvinyl-sulfonyl)-piperazin-1-yl]-2-(4-amidinophenyl)-4-oxo-buttersäure.

Beispiel 13

20

Durch Umsetzung äquimolarer Mengen "A" und Phenylisocyanat in Dichlormethan bei Raumtemperatur erhält man nach üblicher Aufarbeitung die Verbindung 4-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-benzoyl]-piperazin-1-carbonsäure-N-phenyl-amid.

25

Analog erhält man durch Umsetzung von "A"

mit 4-Trifluormethylphenylisocyanat

4-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-benzoyl]-piperazin-1-carbonsäure-N-(4-trifluormethylphenyl)-amid;

30

mit Butylisocyanat

4-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-benzoyl]-piperazin-1-carbonsäure-N-butyl-amid;

35

mit 1-Naphthylisocyanat

4-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-benzoyl]-piperazin-1-carbonsäure-N-(1-naphthyl)-amid;

mit 4-Methoxyphenylisocyanat

4-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-benzoyl]-piperazin-1-carbonsäure-N-(4-methoxyphenyl)-amid;

5

mit 4-Nitrophenylisocyanat

4-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-benzoyl]-piperazin-1-carbonsäure-N-(4-nitrophenyl)-amid;

10

mit Cyclohexylisocyanat

4-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-benzoyl]-piperazin-1-carbonsäure-N-cyclohexyl-amid;

mit 3-Ethoxycarbonylphenylisocyanat

15

4-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-benzoyl]-piperazin-1-carbonsäure-N-(3-ethoxycarbonylphenyl)-amid.

Durch Hydrierung analog Beispiel 2 erhält man daraus die nachstehenden Amidinderivate

20

4-(4-Amidino-benzoyl)-piperazin-1-carbonsäure-N-phenyl-amid, Acetat, FAB 352;

4-(4-Amidino-benzoyl)-piperazin-1-carbonsäure-N-butyl-amid, Acetat, FAB 332;

25

4-(4-Amidino-benzoyl)-piperazin-1-carbonsäure-N-(1-naphthyl)-amid, Acetat, FAB 402;

4-(4-Amidino-benzoyl)-piperazin-1-carbonsäure-N-(4-methoxyphenyl)-amid, Acetat, FAB 382;

4-(4-Amidino-benzoyl)-piperazin-1-carbonsäure-N-(4-aminophenyl)-amid, Acetat, FAB 367;

30

4-(4-Amidino-benzoyl)-piperazin-1-carbonsäure-N-cyclohexyl-amid, Acetat, FAB 358;

4-(4-Amidino-benzoyl)-piperazin-1-carbonsäure-N-(3-ethoxycarbonylphenyl)-amid, Acetat, FAB 424.

35

Beispiel 14

Analog Beispiel 1 und 2 erhält man die nachstehenden Verbindungen

5

3-[4-(2-Naphthylsulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 423;

3-[4-(3-chlor-4-methylphenyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 421;

10

3-[4-(2,4,6-trichlorphenyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 475,477;

3-[4-(3-amino-4-chlorphenyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 422;

15

3-[4-(4-chlor-phenyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 407;

3-[4-(3-trifluormethyl-phenyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 441;

3-[4-(4-biphenyl-yl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 449;

20

4-[4-(3,5-Dimethoxyphenyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 433;

4-[4-(Dibenzofuran-2-yl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 463;

25

4-[4-(3-Fluor-4-methoxyphenyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 421;

4-[4-(2,4-Dichlor-6-methoxyphenyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 471;

30

4-(4-Benzylpiperazin-1-carbonyl)-benzamidin, Acetat, FAB 323;

4-[4-(2-Naphthylmethyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 373;

4-[4-(4-Methoxyphenylmethyl)-piperazin-1-carbonyl]-benzamidin, Diacetat, FAB 353;

4-[4-(4-Methoxycarbonylphenyl-sulfonyl)-piperazin-1-carbonyl]-benzamidin, Acetat, FAB 431;

35

4-[4-(4-Propylphenyl-sulfonyl)-piperazin-1-carbonyl]-3-methylbenzamidin, Acetat, FAB 429;

4-[4-(2-Naphthyl-sulfonyl)-piperazin-1-carbonyl]-3-methyl-benzamidin,
Acetat, FAB 437;

4-[4-(6-Chlor-2-naphthyl-sulfonyl)-piperazin-1-carbonyl]-3-methyl-
benzamidin, Acetat, FAB 471;

5 4-[4-(7-Methoxy-2-naphthyl-sulfonyl)-piperazin-1-carbonyl]-benz-
amidin, Acetat, FAB 453;

4-[4-(3,5-Dimethoxyphenylmethyl)-piperazin-1-carbonyl]-benzamidin,
Acetat, FAB 383;

10 Beispiel 15

Analog Beispiel 6 erhält man die nachstehenden Verbindungen

15 4-{3-Oxo-3-[4-(butylsulfonyl)-piperazin-1-yl]-propyl}-benzamidin,
Acetat, FAB 381;

4-{3-Oxo-3-[4-(4-propylphenyl-sulfonyl)-piperazin-1-yl]-propyl}-
benzamidin, Acetat, FAB 443;

4-{3-Oxo-3-[4-(6-chlor-2-naphthyl-sulfonyl)-piperazin-1-yl]-propyl}-
benzamidin, Acetat, FAB 485;

20 4-{3-Oxo-3-[4-(2-naphthyl-sulfonyl)-piperazin-1-yl]-propyl}-
benzamidin, Acetat, FAB 451;

4-{3-Oxo-3-[4-(3-chlor-4-methylphenyl-sulfonyl)-piperazin-1-yl]-
propyl}-benzamidin, Acetat, FAB 449;

25 4-{3-Oxo-3-[4-(4-chlor-phenyl-sulfonyl)-piperazin-1-yl]-propyl}-
benzamidin, Acetat, FAB 435;

4-{3-Oxo-3-[4-(4-biphenyl-yl-sulfonyl)-piperazin-1-yl]-propyl}-
benzamidin, Acetat, FAB 477;

4-{3-Oxo-3-[4-(2,4,6-trimethyl-phenyl-sulfonyl)-piperazin-1-yl]-propyl}-
benzamidin, Acetat, FAB 443;

30 3-{3-Oxo-3-[4-(butylsulfonyl)-piperazin-1-yl]-propyl}-benzamidin,
Acetat, FAB 381;

3-{3-Oxo-3-[4-(4-methoxyphenyl-sulfonyl)-piperazin-1-yl]-propyl}-
benzamidin, Acetat, FAB 431;

35 3-{3-Oxo-3-[4-(4-chlorphenyl-sulfonyl)-piperazin-1-yl]-propyl}-
benzamidin, Acetat, FAB 435;

3-{3-Oxo-3-[4-(4-isopropylphenyl-sulfonyl)-piperazin-1-yl]-propyl}-
benzamidin, Acetat, FAB 443;

3-{3-Oxo-3-[4-(2,4,6-trimethylphenyl-sulfonyl)-piperazin-1-yl]-propyl}-
benzamidin, Acetat, FAB 443;

5 3-{3-Oxo-3-[4-(3-chlor-4-methylphenyl-sulfonyl)-piperazin-1-yl]-
propyl}-benzamidin, Acetat, FAB 449;

3-{3-Oxo-3-[4-(6-chlor-2-naphthyl-sulfonyl)-piperazin-1-yl]-propyl}-
benzamidin, Acetat, FAB 485;

10 3-{3-Oxo-3-[4-(2-naphthyl-sulfonyl)-piperazin-1-yl]-propyl}-
benzamidin, Acetat, FAB 451;

3-{3-Oxo-3-[4-(4-biphenyl-yl-sulfonyl)-piperazin-1-yl]-propyl}-
benzamidin, Acetat, FAB 477;

Beispiel 16

15

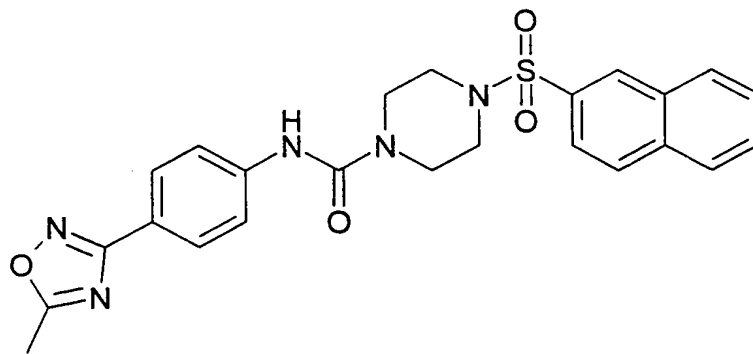
Analog Beispiel 13 erhält man durch Umsetzung von 4-(5-Methyl-[1,2,4]-
oxadiazol-3-yl)-phenylisocyanat ("F")

mit 1-(2-Naphthyl-sulfonyl)-piperazin

20

4-(2-Naphthyl-sulfonyl)-piperazin-1-carbonsäure-N-[4-(5-methyl-
[1,2,4]-oxadiazol-3-yl)-phenyl]-amid

25



30

mit 1-(2-Phenylvinyl-sulfonyl)-piperazin

4-(2-Phenylvinyl-sulfonyl)-piperazin-1-carbonsäure-N-[4-(5-methyl-
[1,2,4]-oxadiazol-3-yl)-phenyl]-amid;

35

mit 1-(4-Propylphenyl-sulfonyl)-piperazin

4-(4-Propylphenyl-sulfonyl)-piperazin-1-carbonsäure-N-[4-(5-methyl-
[1,2,4]-oxadiazol-3-yl)-phenyl]-amid;

mit 1-(4-Chlorphenyl-sulfonyl)-piperazin

5 4-(4-Chlorphenyl-sulfonyl)-piperazin-1-carbonsäure-N-[4-(5-methyl-
[1,2,4]-oxadiazol-3-yl)-phenyl]-amid;

mit 1-(2,4,6-Trimethylphenyl-sulfonyl)-piperazin

10 4-(2,4,6-Trimethylphenyl-sulfonyl)-piperazin-1-carbonsäure-N-[4-(5-
methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-amid;

mit 1-(6-Chlor-2-naphthyl-sulfonyl)-piperazin

15 4-(6-Chlor-2-naphthyl-sulfonyl)-piperazin-1-carbonsäure-N-[4-(5-
methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-amid.

Durch Hydrierung analog Beispiel 2 erhält man daraus die nachstehenden
Amidinderivate

20 4-(2-Naphthyl-sulfonyl)-piperazin-1-carbonsäure-N-(4-amidino-
phenyl)-amid, Acetat, FAB 438;

4-(2-Phenylvinyl-sulfonyl)-piperazin-1-carbonsäure-N-(4-amidino-
phenyl)-amid, Acetat, FAB 414;

4-(4-Propylphenyl-sulfonyl)-piperazin-1-carbonsäure-N-(4-amidino-
phenyl)-amid, Acetat, FAB 430;

25 4-(4-Chlorphenyl-sulfonyl)-piperazin-1-carbonsäure-N-(4-amidino-
phenyl)-amid, Acetat, FAB 422;

4-(2,4,6-Trimethylphenyl-sulfonyl)-piperazin-1-carbonsäure-N-(4-
amidino-phenyl)-amid, Acetat, FAB 430;

30 4-(6-Chlor-2-naphthyl-sulfonyl)-piperazin-1-carbonsäure-N-(4-
amidino-phenyl)-amid, Acetat, FAB 472.

Beispiel 17

35 Analog Beispiel 1 erhält man durch Umsetzung von 1-[4-(5-Methyl-
[1,2,4]oxadiazol-3-yl)-benzyl]-piperazin ("G")

mit 4-Propylphenyl-sulfonylchlorid

1-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-benzyl]-4-(4-propylphenyl-sulfonyl)-piperazin;

5 mit 4-Methoxyphenyl-sulfonylchlorid

1-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-benzyl]-4-(4-methoxyphenyl-sulfonyl)-piperazin;

mit 4-Biphenylyl-sulfonylchlorid

10 1-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-benzyl]-4-(4-biphenylyl-sulfonyl)-piperazin;

mit 2-Naphthyl-sulfonylchlorid

15 1-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-benzyl]-4-(2-naphthyl-sulfonyl)-piperazin;

mit 6-Chlor-2-naphthyl-sulfonylchlorid

20 1-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-benzyl]-4-(6-chlor-2-naphthyl-sulfonyl)-piperazin;

mit 7-Methoxy-2-naphthyl-sulfonylchlorid

1-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-benzyl]-4-(7-methoxy-2-naphthyl-sulfonyl)-piperazin;

25 mit 3,5-Dimethoxybenzylchlorid

1-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-benzyl]-4-(3,5-dimethoxybenzyl)-piperazin;

mit 4-Isopropylphenyl-sulfonylchlorid

30 1-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-benzyl]-4-(4-isopropylphenyl-sulfonyl)-piperazin;

mit 4-Biphenylyl-carbonsäurechlorid

35 1-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-benzyl]-4-(4-biphenylyl-carbonyl)-piperazin;

mit 2-Naphthyl-carbonsäurechlorid

1-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-benzyl]-4-(2-naphthyl-carbonyl)-piperazin;

5 mit 2-Naphthylmethylchlorid

1-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-benzyl]-4-(2-naphthylmethyl)-piperazin.

10 Durch Hydrierung analog Beispiel 2 erhält man daraus die nachstehenden Amidinderivate

1-(4-Amidinobenzyl)-4-(4-propylphenyl-sulfonyl)-piperazin, Acetat, FAB 401;

15 1-(4-Amidinobenzyl)-4-(4-methoxyphenyl-sulfonyl)-piperazin, Acetat, FAB 389;

1-(4-Amidinobenzyl)-4-(4-biphenyl-sulfonyl)-piperazin, Acetat, FAB 435;

1-(4-Amidinobenzyl)-4-(2-naphthyl-sulfonyl)-piperazin, Acetat, FAB 409;

20 1-(4-Amidinobenzyl)-4-(6-chlor-2-naphthyl-sulfonyl)-piperazin, Acetat, FAB 443;

1-(4-Amidinobenzyl)-4-(7-methoxy-2-naphthyl-sulfonyl)-piperazin, Acetat, FAB 439;

25 1-(4-Amidinobenzyl)-4-(3,5-dimethoxybenzyl)-piperazin, Acetat, FAB 369;

1-(4-Amidinobenzyl)-4-(4-isopropylphenyl-sulfonyl)-piperazin, Acetat, FAB 441;

1-(4-Amidinobenzyl)-4-(4-biphenyl-carbonyl)-piperazin, Diacetat, FAB 399;

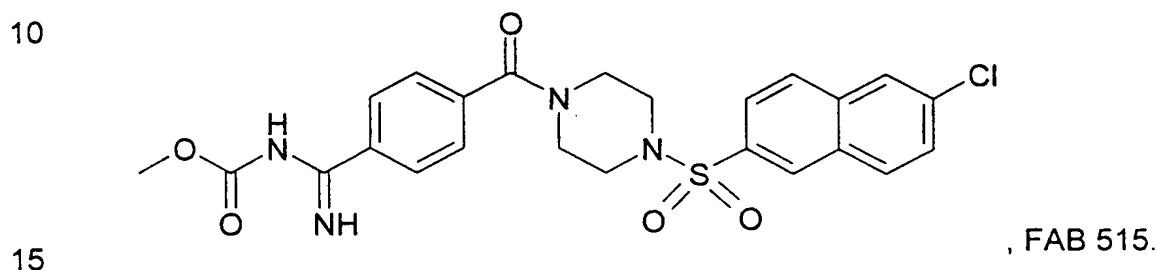
30 1-(4-Amidinobenzyl)-4-(2-naphthyl-carbonyl)-piperazin, Diacetat, FAB 373;

1-(4-Amidinobenzyl)-4-(2-naphthylmethyl)-piperazin, Diacetat, FAB 359.

35

Beispiel 18

5 Durch Umsetzung von 4-[4-(6-Chlor-2-Naphthyl-sulfonyl)-piperazin-1-carbonyl]-3-methyl-benzamidin mit Chlorameisensäuremethylester in Dichlormethan erhält man nach üblicher Aufarbeitung die Verbindung (Imino-{4-[4-(6-Chlor-2-naphthyl-sulfonyl)-piperazin-1-carbonyl]-phenyl}-methyl)-carbaminsäuremethylester



Beispiel 19

20 Analog Beispiel 1 erhält man durch Umsetzung von 1-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-piperazin ("H")

mit 4-Propylphenyl-sulfonylchlorid

1-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-4-(4-propylphenyl-sulfonyl)-piperazin;

25 mit 4-Butyl-sulfonylchlorid

1-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-4-(4-butyl-sulfonyl)-piperazin;

30 mit 4-Methoxyphenyl-sulfonylchlorid

1-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-4-(4-methoxyphenyl-sulfonyl)-piperazin;

mit 4-Chlorphenyl-sulfonylchlorid

35 1-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-4-(4-chlorphenyl-sulfonyl)-piperazin;

mit 4-Isopropylphenyl-sulfonylchlorid

1-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-4-(4-isopropylphenyl-sulfonyl)-piperazin;

5 mit 4-Biphenyl-yl-sulfonylchlorid

1-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-4-(4-biphenylphenyl-sulfonyl)-piperazin;

mit 2,4,6-Trimethylphenyl-sulfonylchlorid

10 1-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-4-(2,4,6-trimethylphenyl-sulfonyl)-piperazin;

mit 3-Chlor-4-methylphenyl-sulfonylchlorid

15 1-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-4-(3-chlor-4-methylphenyl-sulfonyl)-piperazin;

mit 2-Naphthyl-sulfonylchlorid

1-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-4-(2-naphthyl-sulfonyl)-piperazin;

20

mit 6-Chlor-2-naphthyl-sulfonylchlorid

1-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-4-(6-chlor-2-naphthyl-sulfonyl)-piperazin.

25 Durch Hydrierung analog Beispiel 2 erhält man daraus die nachstehenden Amidinderivate

1-(4-Amidinophenyl)-4-(4-propylphenyl-sulfonyl)-piperazin, Acetat, FAB 387;

30 1-(4-Amidinophenyl)-4-(4-butyl-sulfonyl)-piperazin, Acetat, FAB 325;
1-(4-Amidinophenyl)-4-(4-methoxyphenyl-sulfonyl)-piperazin, Acetat, FAB 375;

1-(4-Amidinophenyl)-4-(4-chlorphenyl-sulfonyl)-piperazin, Acetat, FAB 379;

35 1-(4-Amidinophenyl)-4-(4-isopropylphenyl-sulfonyl)-piperazin, Acetat, FAB 387;

1-(4-Amidinophenyl)-4-(4-biphenylphenyl-sulfonyl)-piperazin, Acetat
FAB 421;

1-(4-Amidinophenyl)-4-(2,4,6-trimethylphenyl-sulfonyl)-piperazin,
Acetat, FAB 387;

5 1-(4-Amidinophenyl)-4-(3-chlor-4-methylphenyl-sulfonyl)-piperazin,
Acetat, FAB 393;

1-(4-Amidinophenyl)-4-(2-naphthyl-sulfonyl)-piperazin, Acetat, FAB
395;

10 1-(4-Amidinophenyl)-4-(6-chlor-2-naphthyl-sulfonyl)-piperazin, Acetat,
FAB 429.

15

20

25

30

35

Die nachfolgenden Beispiele betreffen pharmazeutische Zubereitungen:

Beispiel A: Injektionsgläser

5 Eine Lösung von 100 g eines Wirkstoffes der Formel I und 5 g Dinatriumhydrogenphosphat wird in 3 l zweifach destilliertem Wasser mit 2 n Salzsäure auf pH 6,5 eingestellt, steril filtriert, in Injektionsgläser abgefüllt, unter sterilen Bedingungen lyophilisiert und steril verschlossen. Jedes Injektionsglas enthält 5 mg Wirkstoff.

10

Beispiel B: Suppositorien

Man schmilzt ein Gemisch von 20 g eines Wirkstoffes der Formel I mit 100 g Sojalecithin und 1400 g Kakaobutter, gießt in Formen und läßt erkalten. Jedes Suppositorium enthält 20 mg Wirkstoff.

15

Beispiel C: Lösung

20 Man bereitet eine Lösung aus 1 g eines Wirkstoffes der Formel I, 9,38 g $\text{NaH}_2\text{PO}_4 \cdot 2 \text{H}_2\text{O}$, 28,48 g $\text{Na}_2\text{HPO}_4 \cdot 12 \text{H}_2\text{O}$ und 0,1 g Benzalkoniumchlorid in 940 ml zweifach destilliertem Wasser. Man stellt auf pH 6,8 ein, füllt auf 1 l auf und sterilisiert durch Bestrahlung. Diese Lösung kann in Form von Augentropfen verwendet werden.

25

Beispiel D: Salbe

Man mischt 500 mg eines Wirkstoffes der Formel I mit 99,5 g Vaseline unter aseptischen Bedingungen.

30

Beispiel E: Tabletten

Ein Gemisch von 1 kg Wirkstoff der Formel I, 4 kg Lactose, 1,2 kg Kartoffelstärke, 0,2 kg Talk und 0,1 kg Magnesiumstearat wird in üblicher Weise zu Tabletten verpreßt, derart, daß jede Tablette 10 mg Wirkstoff enthält.

35

Beispiel F: Dragees

5 Analog Beispiel E werden Tabletten gepreßt, die anschließend in üblicher Weise mit einem Überzug aus Saccharose, Kartoffelstärke, Talk, Tragant und Farbstoff überzogen werden.

Beispiel G: Kapseln

10 2 kg Wirkstoff der Formel I werden in üblicher Weise in Hartgelatine-kapseln gefüllt, so daß jede Kapsel 20 mg des Wirkstoffs enthält.

Beispiel H: Ampullen

15 Eine Lösung von 1 kg Wirkstoff der Formel I in 60 l zweifach destilliertem Wasser wird steril filtriert, in Ampullen abgefüllt, unter sterilen Bedingungen lyophilisiert und steril verschlossen. Jede Ampulle enthält 10 mg Wirkstoff.

20

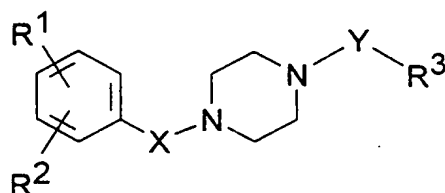
25

30

35

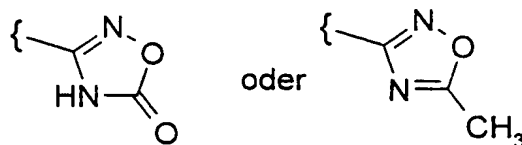
Patentansprüche

1. Verbindungen der Formel I



worin

R^1 $-C(=NH)-NH_2$, das auch einfach durch $-COA$, $-CO-[C(R^6)_2]_n-Ar$, $-COOA$, $-OH$ oder durch eine konventionelle Aminoschutzgruppe substituiert sein kann,



R^2 H, A, OR^6 , $N(R^6)_2$, NO_2 , CN, Hal, $NHCOA$, $NHCOAr$, $NHSO_2A$, $NHSO_2Ar$, $COOR^6$, $CON(R^6)_2$, $CONHAr$, COR^6 , $COAr$, $S(O)_nA$ oder $S(O)_nAr$,

R^3 A, Cycloalkyl, $-[C(R^6)_2]_nAr$, $-[C(R^6)_2]_n-O-Ar$, $-[C(R^6)_2]_nHet$ oder $-C(R^6)_2=C(R^6)_2-Ar$,

R^6 H, A oder Benzyl,

X fehlt, $-CO-$, $-C(R^6)_2-$, $-C(R^6)_2-C(R^6)_2-$, $-C(R^6)_2-CO-$, $-C(R^6)_2-C(R^6)_2-CO-$, $-C(R^6)=C(R^6)-CO-$, NR^6CO- , $-N\{[C(R^6)_2]_n-COOR^6\}-CO-$ oder $-C(COOR^6)R^6-C(R^6)_2-CO-$,

	Y	$-C(R^6)_2-$, $-SO_2-$, $-CO-$, $-COO-$ oder $-CONR^6-$,
5	A	Alkyl mit 1-20 C-Atomen, worin eine oder zwei CH_2 -Gruppen durch O- oder S-Atome oder durch $-CR^6=CR^6-$ Gruppen und/oder 1-7 H-Atome durch F ersetzt sein können,
10	Ar	unsubstituiertes oder ein-, zwei- oder dreifach durch A, Ar' , OR^6 , $N(R^6)_2$, NO_2 , CN, Hal, $NHCOA$, $NHCOAr'$, $NHSO_2A$, $NHSO_2Ar'$, $COOR^6$, $CON(R^6)_2$, $CONHAr'$, COR^6 , $COAr'$, $S(O)_nA$ oder $S(O)_nAr$ substituiertes Phenyl oder Naphthyl,
15	Ar'	unsubstituiertes oder ein-, zwei- oder dreifach durch A, OR^6 , $N(R^6)_2$, NO_2 , CN, Hal, $NHCOA$, $COOR^6$, $CON(R^6)_2$, COR^6 , oder $S(O)_nA$ substituiertes Phenyl oder Naphthyl,
20	Het	ein- oder zweikerniges unsubstituiertes oder ein- oder mehrfach durch Hal, A, Ar' , $COOR^6$, CN, $N(R^6)_2$, NO_2 , $Ar-CONH-CH_2$ und/oder Carbonylsauerstoff substituiertes gesättigtes oder ungesättigtes heterocyclisches
25		Ringsystem, welches eines, zwei, drei oder vier gleiche oder verschiedene Heteroatome wie Stickstoff, Sauerstoff und Schwefel enthält,
30	Hal	F, Cl, Br oder I,
	n	0, 1 oder 2 bedeutet,
35		sowie deren Salze.

2. Verbindungen gemäß Anspruch 1

- 5 a) 4-[4-(4-Propylphenylsulfonyl)-1-piperazinylcarbonyl]-benzamidin;
 b) 4-[4-(3-Amino-4-chlorphenylsulfonyl)-1-piperazinylcarbonyl]-benzamidin;
 c) 4-[4-(6-Chlornaphthalin-2-sulfonyl)-1-piperazinylcarbonyl]-benzamidin;
 10 d) 4-[4-(2-Phenylvinylsulfonyl)-1-piperazinylcarbonyl]-benzamidin;

sowie deren Salze.

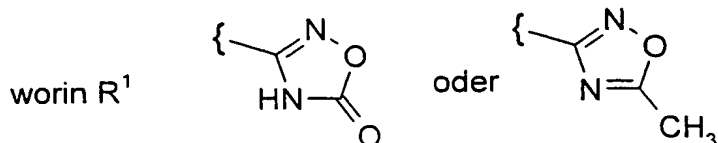
15 3. Verfahren zur Herstellung von Verbindungen der Formel I nach Anspruch 1 sowie ihrer Salze, dadurch gekennzeichnet, daß man

- a) sie aus einem ihrer funktionellen Derivate durch Behandeln mit einem solvolysierenden oder hydrogenolysierenden Mittel in Freiheit setzt, indem man
- 20 i) eine Amidinogruppe aus ihrem Oxadiazolderivat durch Hydrogenolyse freisetzt,
- ii) eine konventionelle Aminoschutzgruppe durch Behandeln mit einem solvolysierenden oder hydrogenolysierenden Mittel durch Wasserstoff ersetzt oder eine durch eine konventionelle Schutzgruppe geschützte Aminogruppe in Freiheit setzt,

30 oder

- b) daß man zur Herstellung von Verbindungen der Formel I,

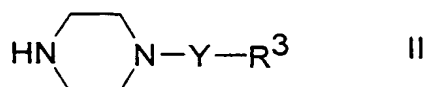
35



X -CO- oder -C(R⁶)₂-CO-,
und R², R³ und Y die in Anspruch 1 angegebenen Bedeutungen
haben,

5

eine Verbindung der Formel II



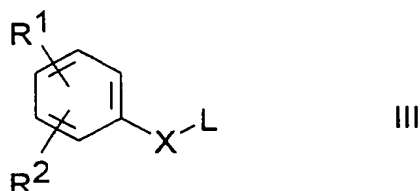
10

worin

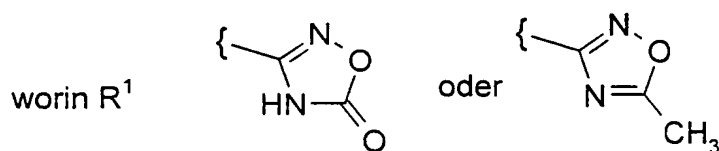
R³ und Y die in Anspruch 1 angegebenen Bedeutungen haben,

15

mit einer Verbindung der Formel III



20



25

X -CO- oder -C(R⁶)₂-CO- bedeutet,

R² die in Anspruch 1 angegebene Bedeutung hat,

30

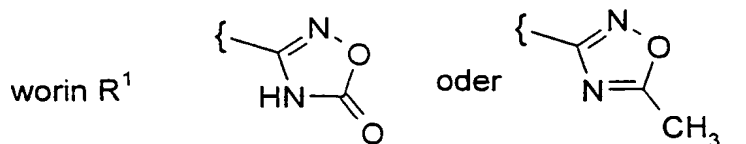
und L Cl, Br, I oder eine freie oder reaktionsfähig funktionell
abgewandelte OH-Gruppe bedeutet,

umsetzt,

35

oder

c) daß man zur Herstellung von Verbindungen der Formel I,



Y -SO₂-, -CO-, -COO- oder -C(R⁶)₂- bedeutet,
und R² und X die in Anspruch 1 angegebenen Bedeutungen
haben,

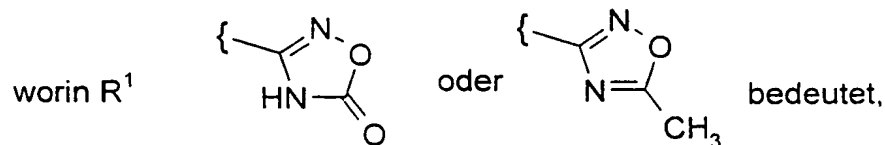
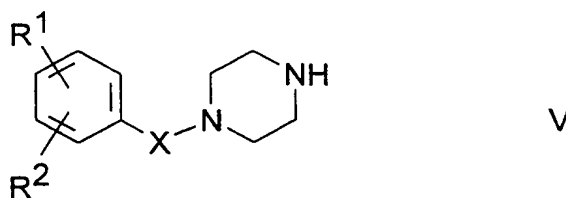
eine Verbindung der Formel IV



worin

Y -SO₂-, -CO-, -COO- oder -C(R⁶)₂- bedeutet,
R³ die in Anspruch 1 angegebene Bedeutung hat,
und L Cl, Br, I oder eine freie oder reaktionsfähig funktionell
abgewandelte OH-Gruppe bedeutet,

mit einer Verbindung der Formel V



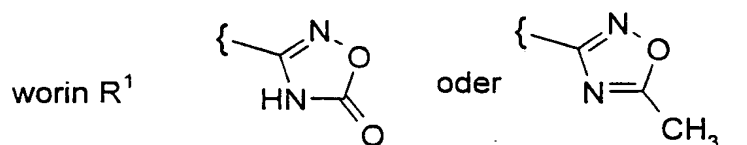
und R² und X die in Anspruch 1 angegebenen Bedeutungen
haben,

umsetzt,

oder

d) daß man zur Herstellung von Verbindungen der Formel I,

5



10

Y -CONH- bedeutet,
und R² und X die in Anspruch 1 angegebenen Bedeutungen
haben,

eine Verbindung der Formel VI

15

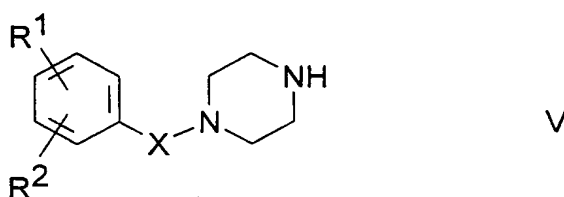


worin R³ die in Anspruch 1 angegebene Bedeutung hat,

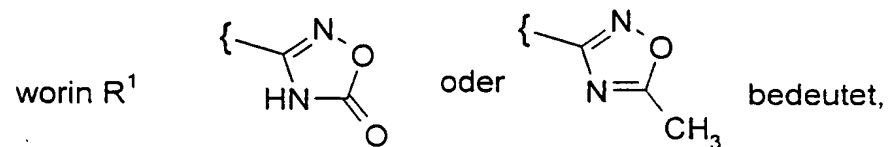
20

mit einer Verbindung der Formel V

25



30



und R² und X die in Anspruch 1 angegebenen Bedeutungen
haben,

umsetzt,

35

oder

- e) daß man zur Herstellung von Verbindungen der Formel I,
worin R^1 $-C(=NH)-NH_2$ bedeutet,
5 eine Cyangruppe in eine Amidinogruppe umwandelt,
- f) und/oder daß man in einer Verbindung der Formel I einen oder
mehrere Rest(e) R^1 , R^2 und/oder R^3 in einen oder mehrere
Rest(e) R^1 , R^2 und/oder R^3 umwandelt,
10 indem man beispielsweise
- i) eine Estergruppe zu einer Carboxygruppe hydrolysiert,
15 ii) eine Nitrogruppe reduziert,
iii) eine Aminogruppe acyliert,
- g) und/oder eine Base oder Säure der Formel I in eines ihrer Salze
20 umwandelt.
4. Verfahren zur Herstellung pharmazeutischer Zubereitungen, dadurch
gekennzeichnet, daß man eine Verbindung der Formel I nach An-
spruch 1 und/oder eines ihrer physiologischen unbedenklichen Salze
25 zusammen mit mindestens einem festen, flüssigen oder halb-
flüssigen Träger- oder Hilfsstoff in eine geeignete Dosierungsform
bringt.
5. Pharmazeutische Zubereitung, gekennzeichnet durch einen Gehalt
30 an mindestens einer Verbindung der Formel I nach Anspruch 1
und/oder einem ihrer physiologisch unbedenklichen Salze.
6. Verbindungen der Formel I nach Anspruch 1 und ihre physiologisch
unbedenklichen Salze zur Bekämpfung von Thrombosen, myocardia-
lem Infarkt, Arteriosklerose, Entzündungen, Apoplexie, Angina pecto-
35 ris, Restenose nach Angioplastie und Claudicatio intermittens.

7. Arzneimittel der Formel I nach Anspruch 1 und ihre physiologisch unbedenklichen Salze als Inhibitoren des Koagulationsfaktors Xa.
- 5 8. Verwendung von Verbindungen der Formel I nach Anspruch 1 und/oder ihre physiologisch unbedenklichen Salze zur Herstellung eines Arzneimittels.
- 10 9. Verwendung von Verbindungen der Formel I nach Anspruch 1 und/oder ihrer physiologisch unbedenklichen Salze bei der Bekämpfung von Thrombosen, myocardialem Infarkt, Arteriosklerose, Entzündungen, Apoplexie, Angina pectoris, Restenose nach Angioplastie und Claudicatio intermittens.

15

20

25

30

35

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/05898

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D213/81 A61K31/495 C07D271/06 C07D295/22 C07D295/20
 C07D333/34 C07D215/36 C07D311/74 C07D333/38 C07D213/18
 C07D261/10 C07D333/70 C07D317/68 C07D413/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>EP 0 608 759 A (MERCK PATENT G.M.B.H.; GERMANY) 3 August 1994 see abstract; claims see page 3, line 1 - line 12 see page 9; example 1 see page 13 - page 14; examples 5,6 --- -/--</p>	1-9



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

15 February 1999

Date of mailing of the international search report

25/02/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Paisdor, B

INTERNATIONAL SEARCH REPORT

 International Application No
 PCT/EP 98/05898

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>ELDRED C D ET AL: "Orally Active Non-Peptide Fibrinogen Receptor (GpIIb/IIIa) Antagonists: Identification of 4-(4-(4-(Aminoimino methyl)phenyl)-1-piperazinyl)-1-piperidineacetic Acid as a Long-Acting, Broad-Spectrum Antithrombotic Agent"</p> <p>J. MED. CHEM. (JMCMAR,00222623);94; VOL.37 (23); PP.3882-5, XP000579663</p> <p>Glaxo Group Research Ltd.;Department of Medicinal Chemistry; Ware / Hertfordshire; SG12 ODP; UK (GB)</p> <p>see page 3883 - page 3884; tables 1-3</p> <p>see abstract</p> <p>---</p>	1-9
A	<p>STUERZEBECKER J ET AL: "Synthesis and Structure-Activity Relationships of Potent Thrombin Inhibitors: Piperazides of 3-Amidinophenylalanine"</p> <p>J. MED. CHEM. (JMCMAR,00222623);97; VOL.40 (19); PP.3091-3099, XP002077904</p> <p>Zentrum fuer Vaskulaere Biologie und Medizin;Klinikum der Friedrich-Schiller-Universitaet Jena; Erfurt; D-99089; Germany (DE)</p> <p>see abstract</p> <p>see page 3093; table 2</p> <p>see page 3094; table 4</p> <p>---</p>	1-9
A	<p>WO 93 22303 A (GLAXO GROUP LTD.;UK)</p> <p>11 November 1993</p> <p>see abstract; claim 1</p> <p>see page 1 - page 3</p> <p>---</p>	1-9
A	<p>WO 92 08709 A (PENTAPHARM AG) 29 May 1992</p> <p>see abstract; claims</p> <p>see page 94 - page 100; tables 19-26</p> <p>---</p>	1-9
A	<p>EP 0 540 051 A (DAIICHI PHARMACEUTICAL CO., LTD.) 5 May 1993</p> <p>cited in the application</p> <p>see abstract; claims</p> <p>see page 58; example 1</p> <p>see page 3, line 1-7</p> <p>-----</p>	1-9

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 98/05898

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 9
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although Claim 9 relates to a method for treating the human/animal body, the search was carried out and was based on the cited effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP98/05898

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0608759	A	03-08-1994	DE 4302485 A	04-08-1994
			AU 670649 B	25-07-1996
			AU 5470294 A	04-08-1994
			CA 2114361 A	30-07-1994
			CN 1099759 A	08-03-1995
			CZ 9400163 A	17-08-1994
			HU 70042 A	28-09-1995
			JP 6271549 A	27-09-1994
			NO 940308 A	01-08-1994
			PL 302069 A	08-08-1994
			SK 6894 A	10-08-1994
			ZA 9400615 A	13-09-1994
WO 9322303	A	11-11-1993	AU 4261293 A	29-11-1993
			CN 1083475 A	09-03-1994
			EP 0637304 A	08-02-1995
			JP 7505897 T	29-06-1995
			MX 9302283 A	28-02-1994
			ZA 9302790 A	25-03-1994
WO 9208709	A	29-05-1992	AU 8868991 A	11-06-1992
			CA 2073776 A	16-05-1992
			EP 0511347 A	04-11-1992
			JP 5503300 T	03-06-1993
			US 5518735 A	21-05-1996
EP 0540051	A	05-05-1993	AT 136293 T	15-04-1996
			AU 666137 B	01-02-1996
			AU 2747092 A	06-05-1993
			CA 2081836 A	01-05-1993
			CN 1072677 A	02-06-1993
			CN 1168885 A	31-12-1997
			CN 1168886 A	31-12-1997
			CZ 284381 B	11-11-1998
			DE 69209615 D	09-05-1996
			DE 69209615 T	09-01-1997
			DK 540051 T	06-05-1996
			ES 2088073 T	01-08-1996
			FI 924932 A	01-05-1993
			GR 3019832 T	31-08-1996
			HR 921147 A	31-10-1995
			HU 65890 A	28-07-1994
			JP 10291931 A	04-11-1998
			JP 5208946 A	20-08-1993
			MX 9206295 A	01-08-1993
			NO 302948 B	11-05-1998
			NZ 244936 A	26-05-1995
			PL 170312 B	29-11-1996
			US 5576343 A	19-11-1996
			US 5620991 A	15-04-1997
			ZA 9208276 A	06-05-1993

INTERNATIONAL RECHERCHENBERICHT

nationales Aktenzeichen

PCT/EP 98/05898

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES

IPK 6 C07D213/81 A61K31/495 C07D271/06 C07D295/22 C07D295/20
C07D333/34 C07D215/36 C07D311/74 C07D333/38 C07D213/18
C07D261/10 C07D333/70 C07D317/68 C07D413/12

Nach der Internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)

IPK 6 C07D A61K

Recherchierte aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
A	EP 0 608 759 A (MERCK PATENT G.M.B.H.; GERMANY) 3. August 1994 siehe Zusammenfassung; Ansprüche siehe Seite 3, Zeile 1 - Zeile 12 siehe Seite 9; Beispiel 1 siehe Seite 13 - Seite 14; Beispiele 5,6 --- -/-	1-9



Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen



Siehe Anhang Patentfamilie

* Besondere Kategorien von angegebenen Veröffentlichungen :

"A" Veröffentlichung, die den allgemeinen Stand der Technik definiert, aber nicht als besonders bedeutsam anzusehen ist

"E" älteres Dokument, das jedoch erst am oder nach dem internationalen Anmeldedatum veröffentlicht worden ist

"L" Veröffentlichung, die geeignet ist, einen Prioritätsanspruch zweifelhaft erscheinen zu lassen, oder durch die das Veröffentlichungsdatum einer anderen im Recherchenbericht genannten Veröffentlichung belegt werden soll oder die aus einem anderen besonderen Grund angegeben ist (wie ausgeführt)

"O" Veröffentlichung, die sich auf eine mündliche Offenbarung, eine Benutzung, eine Ausstellung oder andere Maßnahmen bezieht

"P" Veröffentlichung, die vor dem internationalen Anmeldedatum, aber nach dem beanspruchten Prioritätsdatum veröffentlicht worden ist

"T" Spätere Veröffentlichung, die nach dem internationalen Anmeldedatum oder dem Prioritätsdatum veröffentlicht worden ist und mit der Anmeldung nicht kollidiert, sondern nur zum Verständnis des der Erfindung zugrundeliegenden Prinzips oder der ihr zugrundeliegenden Theorie angegeben ist

"X" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann allein aufgrund dieser Veröffentlichung nicht als neu oder auf erfinderischer Tätigkeit beruhend betrachtet werden

"Y" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann nicht als auf erfinderischer Tätigkeit beruhend betrachtet werden, wenn die Veröffentlichung mit einer oder mehreren anderen Veröffentlichungen dieser Kategorie in Verbindung gebracht wird und diese Verbindung für einen Fachmann naheliegend ist

"&" Veröffentlichung, die Mitglied derselben Patentfamilie ist

Datum des Abschlusses der internationalen Recherche

15. Februar 1999

Absenddatum des internationalen Recherchenberichts

25/02/1999

Name und Postanschrift der Internationalen Recherchenbehörde
Europäisches Patentamt, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Bevollmächtigter Bediensteter

Paisdor, B

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN		
Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
A	<p>ELDRED C D ET AL: "Orally Active Non-Peptide Fibrinogen Receptor (GpIIb/IIIa) Antagonists: Identification of 4-(4-(4-(Aminoimino methyl)phenyl)-1-piperazinyl)-1-piperidineacetic Acid as a Long-Acting, Broad-Spectrum Antithrombotic Agent" J. MED. CHEM. (JMCMAR,00222623);94; VOL.37 (23); PP.3882-5, XP000579663 Glaxo Group Research Ltd.;Department of Medicinal Chemistry; Ware / Hertfordshire; SG12 ODP; UK (GB) siehe Seite 3883 - Seite 3884; Tabellen 1-3 siehe Zusammenfassung</p>	1-9
A	<p>STUERZEBECHER J ET AL: "Synthesis and Structure-Activity Relationships of Potent Thrombin Inhibitors: Piperazides of 3-Amidinophenylalanine" J. MED. CHEM. (JMCMAR,00222623);97; VOL.40 (19); PP.3091-3099, XP002077904 Zentrum fuer Vaskulaere Biologie und Medizin;Klinikum der Friedrich-Schiller-Universitaet Jena; Erfurt; D-99089; Germany (DE) siehe Zusammenfassung siehe Seite 3093; Tabelle 2 siehe Seite 3094; Tabelle 4</p>	1-9
A	<p>WO 93 22303 A (GLAXO GROUP LTD.;UK) 11. November 1993 siehe Zusammenfassung; Anspruch 1 siehe Seite 1 - Seite 3</p>	1-9
A	<p>WO 92 08709 A (PENTAPHARM AG) 29. Mai 1992 siehe Zusammenfassung; Ansprüche siehe Seite 94 - Seite 100; Tabellen 19-26</p>	1-9
A	<p>EP 0 540 051 A (DAIICHI PHARMACEUTICAL CO., LTD.) 5. Mai 1993 in der Anmeldung erwähnt siehe Zusammenfassung; Ansprüche siehe Seite 58; Beispiel 1 siehe Seite 3, Zeile 1-7</p>	1-9

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen

PCT/EP 98/05898

Feld I Bemerkungen zu den Ansprüchen, die sich als nicht recherchierbar erwiesen haben (Fortsetzung von Punkt 1 auf Blatt 1)

Gemäß Artikel 17(2)a) wurde aus folgenden Gründen für bestimmte Ansprüche kein Recherchenbericht erstellt:

1. ☒ Ansprüche Nr. 9
weil sie sich auf Gegenstände beziehen, zu deren Recherche die Behörde nicht verpflichtet ist, nämlich
Bemerkung: Obwohl Anspruch 9 sich auf ein Verfahren zur Behandlung des menschlichen/tierischen Körpers bezieht, wurde die Recherche durchgeführt und gründete sich auf die angeführten Wirkungen der Verbindung/Zusammensetzung.
2. ☐ Ansprüche Nr.
weil sie sich auf Teile der internationalen Anmeldung beziehen, die den vorgeschriebenen Anforderungen so wenig entsprechen, daß eine sinnvolle internationale Recherche nicht durchgeführt werden kann, nämlich
3. ☐ Ansprüche Nr.
weil es sich dabei um abhängige Ansprüche handelt, die nicht entsprechend Satz 2 und 3 der Regel 6.4 a) abgefaßt sind.

Feld II Bemerkungen bei mangelnder Einheitlichkeit der Erfindung (Fortsetzung von Punkt 2 auf Blatt 1)

Die internationale Recherchenbehörde hat festgestellt, daß diese internationale Anmeldung mehrere Erfindungen enthält:

1. ☐ Da der Anmelder alle erforderlichen zusätzlichen Recherchegebühren rechtzeitig entrichtet hat, erstreckt sich dieser internationale Recherchenbericht auf alle recherchierbaren Ansprüche der internationalen Anmeldung.
2. ☐ Da für alle recherchierbaren Ansprüche die Recherche ohne einen Arbeitsaufwand durchgeführt werden konnte, der eine zusätzliche Recherchegebühr gerechtfertigt hätte, hat die Internationale Recherchenbehörde nicht zur Zahlung einer solchen Gebühr aufgefordert.
3. ☐ Da der Anmelder nur einige der erforderlichen zusätzlichen Recherchegebühren rechtzeitig entrichtet hat, erstreckt sich dieser internationale Recherchenbericht nur auf die Ansprüche der internationalen Anmeldung, für die Gebühren entrichtet worden sind, nämlich auf die Ansprüche Nr.
4. ☐ Der Anmelder hat die erforderlichen zusätzlichen Recherchegebühren nicht rechtzeitig entrichtet. Der internationale Recherchenbericht beschränkt sich daher auf die in den Ansprüchen zuerst erwähnte Erfindung; diese ist in folgenden Ansprüchen erfaßt:

Bemerkungen hinsichtlich eines Widerspruchs

☐ Die zusätzlichen Gebühren wurden vom Anmelder unter Widerspruch gezahlt.☐ Die Zahlung zusätzlicher Gebühren erfolgte ohne Widerspruch.

INTERNATIONALER RECHERCHENBERICHT

Angaben zu Veröffentlichungen, die zu einer Patentfamilie gehören

Internationale Aktenzeichen

PCT/EP/98/05898

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie	Datum der Veröffentlichung
EP 0608759 A	03-08-1994	DE 4302485 A	04-08-1994
		AU 670649 B	25-07-1996
		AU 5470294 A	04-08-1994
		CA 2114361 A	30-07-1994
		CN 1099759 A	08-03-1995
		CZ 9400163 A	17-08-1994
		HU 70042 A	28-09-1995
		JP 6271549 A	27-09-1994
		NO 940308 A	01-08-1994
		PL 302069 A	08-08-1994
		SK 6894 A	10-08-1994
		ZA 9400615 A	13-09-1994
WO 9322303 A	11-11-1993	AU 4261293 A	29-11-1993
		CN 1083475 A	09-03-1994
		EP 0637304 A	08-02-1995
		JP 7505897 T	29-06-1995
		MX 9302283 A	28-02-1994
		ZA 9302790 A	25-03-1994
WO 9208709 A	29-05-1992	AU 8868991 A	11-06-1992
		CA 2073776 A	16-05-1992
		EP 0511347 A	04-11-1992
		JP 5503300 T	03-06-1993
		US 5518735 A	21-05-1996
EP 0540051 A	05-05-1993	AT 136293 T	15-04-1996
		AU 666137 B	01-02-1996
		AU 2747092 A	06-05-1993
		CA 2081836 A	01-05-1993
		CN 1072677 A	02-06-1993
		CN 1168885 A	31-12-1997
		CN 1168886 A	31-12-1997
		CZ 284381 B	11-11-1998
		DE 69209615 D	09-05-1996
		DE 69209615 T	09-01-1997
		DK 540051 T	06-05-1996
		ES 2088073 T	01-08-1996
		FI 924932 A	01-05-1993
		GR 3019832 T	31-08-1996
		HR 921147 A	31-10-1995
		HU 65890 A	28-07-1994
		JP 10291931 A	04-11-1998
		JP 5208946 A	20-08-1993
		MX 9206295 A	01-08-1993
		NO 302948 B	11-05-1998
		NZ 244936 A	26-05-1995
		PL 170312 B	29-11-1996
		US 5576343 A	19-11-1996
		US 5620991 A	15-04-1997
		ZA 9208276 A	06-05-1993

1

2

3



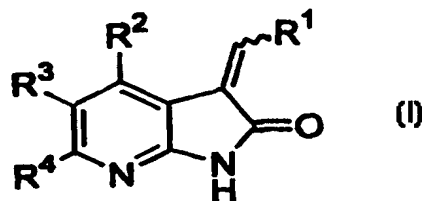
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 471/04, A61K 31/435 // (C07D 471/04, 221:00, 209:00)		A1	(11) International Publication Number: WO 99/21859
			(43) International Publication Date: 6 May 1999 (06.05.99)
(21) International Application Number: PCT/EP98/06357 (22) International Filing Date: 8 October 1998 (08.10.98) (30) Priority Data: 9721437.3 10 October 1997 (10.10.97) GB (71) Applicant (for all designated States except US): GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): CHEUNG, Mui [CN/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US). GLENNON, Kimberly, Caroline [US/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US). LACKEY, Karen, Elizabeth [US/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US). PEEL, Michael, Robert [GB/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US). (74) Agent: REED, Michael, A.; Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	

(54) Title: AZAOXINDOLE DERIVATIVES

(57) Abstract

Compounds of formula (I) where R₁ is optionally substituted phenyl or an optionally substituted phenyl or an optionally substituted heterocyclic ring selected from pyrrole, furan, thiophene, pyrazole or indole are useful as protein kinase inhibitors in diseases characterized by cellular proliferation.



FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

AZAOXINDOLE DERIVATIVES

FIELD OF THE INVENTION

5 The present invention provides novel compounds, novel compositions, methods of their use and methods of their manufacture, such compounds generally pharmacologically useful as agents which inhibit protein kinases, and which compounds can be characterized as substituted pyrrolopyridinones. The pharmacological activities of the claimed compounds are useful in the
10 treatment of mammals, for example in the treatment of psoriasis, fibrosis, atherosclerosis, restenosis, auto-immune disease, allergy, asthma, transplantation rejection, inflammation, thrombosis, nervous system diseases, and cancer.

15 More specifically, the present invention is directed to methods of regulating, modulating, or inhibiting protein kinases of both the receptor and non-receptor types, for the prevention and/or treatment of disorders related to unregulated protein kinase activity, including cell proliferative disorders, metabolic disorders and excessive cytokine production disorders. The compounds of the
20 present invention can also be used in the treatment of certain forms of cancer, can be used to provide additive or synergistic effects with certain existing cancer chemotherapies, and/or be used to restore effectiveness of certain existing cancer chemotherapies and radiation. At the present time, there is a need in the areas of diseases characterized by cell proliferation for such
25 therapeutic agents.

BACKGROUND OF THE INVENTION

Protein kinases play a critical role in the control of cell growth and differentiation (Schlessinger and Ullrich, 1992, Neuron, 9:383-391). A partial
30 non-limiting list of such kinases includes ab1, ATK, bcr-ab1, Blk, Brk, Btk, c-fms, c-kit, c-met, c-src, CDK1, CDK2, CDK4, CDK6, cRaf1, CSF1R, CSK, EGFR, ErbB2, ErbB3, ErbB4, ERK, Fak, fes, FGFR1, FGFR2, FGFR3, FGFR4, FGFR5, Fgr, FLK-4, flt-1, Fps, Frk, Fyn, GSK, Hck, IGF-1R, INS-R, Jak, JNK, KDR, Lck, Lyn, MEK, p38, PDGFR, PIK, PKC, PYK2, ros, tie₁, tie₂,
35 TRK, UL97, VEGFR, Yes and Zap70. Aberrant expression or mutations in

protein kinases have been shown to lead to either uncontrolled cell proliferation (for example, malignant tumour growth) or to defects in key developmental processes. Protein kinases are critical to the control, regulation, and modulation of cell proliferation in the diseases and disorders associated with abnormal cell proliferation, therefore the inhibition of protein kinases is an object of the present invention.

Additionally, protein kinases have been implicated as targets in central nervous system disorders (such as Alzheimer's), inflammatory disorders (such as psoriasis), bone diseases (such as osteoporosis), atheroscleroses, restenosis, thrombosis, metabolic disorders (such as diabetes) and infectious diseases (such as viral and fungal infections).

One of the most commonly studied pathways involving kinase regulation is cellular signalling from receptors at the cell surface to the nucleus (Crews and Erikson, 1993). The function of each receptor kinase is determined by its pattern of expression, ligand availability, and the array of downstream signal transduction pathways that are activated by a particular receptor. One example of this pathway includes a cascade of kinases in which members of the Growth Factor receptor Tyrosine Kinases (such as EGF-R, PDGF-R, VEGF-R, IGF1-R, the Insulin receptor), deliver signals through phosphorylation to other kinases such as Src Tyrosine kinase, and the Raf, Mek and Erk serine/threonine kinase families (Crews and Erikson, 1993; Ihle et al., 1994). Each of these kinases is represented by several family members (Pelech and Sanghera, 1992) which play related, but functionally distinct roles. The loss of regulation of the growth factor signalling pathway is a frequent occurrence in cancer (Fearon, *Genetic lesions in human cancer*, in Molecular Oncology; 1996, 143-178) as well as other disease states.

Ras genes are mutated with the following frequencies such as those in this partial non-limiting list of primary human tumors: lung (adenocarcinoma), 30%; colon (adenocarcinoma), 50%; pancreatic carcinoma, 90%; seminoma, 40%; thyroid, 50% (McCormick, *Ras oncogenes* in *Oncogenes and the molecular origins of cancer*: 1989, 125-146). The raf1 serine/threonine kinase can be activated by the known oncogene product *ras*. The raf kinase enzyme

positively regulates cell division through the Raf/MEK/ERK protein kinase cascade. This activation is the result of cRaf1 catalyzed phosphorylation of the protein kinase, MEK1. MEK1 phosphorylates and activates the protein kinase ERK (alternatively known as p42/MAP kinase protein). ERK phosphorylates and regulates transcription factors required for cell division (Avruch et al, TIBS; 1994 (19) 279-283). cRaf1 negatively regulates cell death by modulation of the activity of Bcl-2, a critical regulator of apoptosis. This regulation involves direct phosphorylation of Bcl-2 family members (Gajewski and Thompson, Cell: 1996 (87) 619-628). Both of these aspects of cRaf1 mediated regulation of cellular proliferation require the kinase activity of cRaf1. In addition, Raf anti-sense literature teaches that the reduction of Raf protein levels correlates with a reduction in tumor growth rate in *vivo* tumor mouse models (Monia, Johnston, Geiger, Muller, and Fabro, Nature Medicine, volume 2, number 6, June 1996, 668-674). Inhibitors of the kinase activity of cRaf1 should therefore provide effective treatment for a wide variety of common human cancers.

Activation of the MAP kinase signalling pathway represents an attractive target for tumor therapy by inhibiting one, or several, of the kinases involved. An additional member of the MAP kinase family of proteins is the p38 kinase (alternatively known as cytokine suppressive drug binding protein [CSBPTM] or reactivation kinase[RK]). Activation of this kinase has been implicated in the production of proinflammatory cytokines such as IL-1 and TNF. Consequently, inhibition of this kinase could offer a treatment for disease states in which disregulated cytokine production is involved.

The signals mediated by kinases have also been shown to control cell growth, cell death and differentiation in the cell by regulating the processes of the cell cycle (Massague and Roberts, 1995). Progression through the eukaryotic cell cycle is controlled by a family of kinases called cyclin dependent kinases (CDKs) (Myerson et al., 1992). The regulation of CDK activation is complex, but requires the association of the CDK with a member of the cyclin family of regulatory subunits (Draetta, 1993; Murray and Kirschner, 1989; Solomon et al., 1992). A further level of regulation occurs through both activating and inactivating phosphorylations of the CDK subunit (Draetta, 1993; Ducommun

et al., 1991; Gautier et al., 1989; Gould and Nurse, 1989; Krek and Nigg, 1991; Murray and Kirschner, 1989; Solomon et al., 1992; Solomon et al., 1990). The coordinate activation and inactivation of different cyclin/CDK complexes is necessary for normal progression through the cell cycle (Pines, 1993; Sherr, 1993). Both the critical G1-S and G2-M transitions are controlled by the activation of different cyclin/CDK activities. In G1, both cyclin D/CDK4 and cyclin E/CDK2 are thought to mediate the onset of S-phase (Matsushime et al., 1994; Ohtsubo and Roberts, 1993; Quelle et al., 1993; Resnitzky et al., 1994). Progression through S-phase requires the activity of cyclin A/CDK2 (Girard et al., 1991; Pagano et al., 1992; Rosenblatt et al., 1992; Walker and Maller, 1991; Zindy et al., 1992) whereas the activation of cyclin A/*cdc2* (CDK1) and cyclin B/*cdc2* are required for the onset of metaphase (Draetta, 1993; Girard et al., 1991; Murray and Kirschner, 1989; Pagano et al., 1992; Rosenblatt et al., 1992; Solomon et al., 1992; Walker and Maller, 1991; Zindy et al., 1992). It is not surprising, therefore, that the loss of control of CDK regulation is a frequent event in hyperproliferative diseases and cancer. (Hunter and Pines, 1994; Lees, 1995; Pines, 1992)

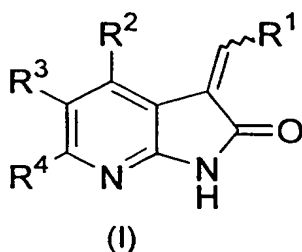
Inhibitors of kinases involved in mediating or maintaining particular disease states represent novel therapies for these disorders. Examples of such kinases include, but are not limited to: (1) inhibition of Src (Brickell, 1992; Courtneidge, 1994), raf (Powis, 1994) and the cyclin-dependent kinases (CDKs) 1, 2 and 4 in cancer (Hunter and Pines, 1994; Lees, 1995; Pines, 1992), (2) inhibition of CDK2 or PDGF-R kinase in restenosis (Buchdunger et al., 1995), (3) inhibition of CDK5 and GSK3 kinases in Alzheimers (Aplin et al., 1996; Hosoi et al., 1995), (4) inhibition of c-Src kinase in osteoporosis (Tanaka et al., 1996), (5) inhibition of GSK-3 kinase in type-2 diabetes (Borthwick et al., 1995); (6) inhibition of the p38 kinase in inflammation (Badger et al., 1996); (7) inhibition of VEGF-R 1-3 and TIE-1 and -2 kinases in angiogenesis (Shawver et al., 1997); (8) inhibition of UL97 kinase in viral infections (He et al., 1997); (9) inhibition of CSF-1R kinase in bone and hematopoietic diseases (Myers et al., 1997), and (10) inhibition of Lck kinase in autoimmune diseases and transplant rejection (Myers et al., 1997).

It is an object of the present invention to provide potent, specific, orally, intravenously, or subcutaneously active small molecule inhibitors of the signal transduction activity of protein kinases for the treatment of human malignancies, for example, one or more of breast, stomach, ovary, colon, lung, brain, larynx, lymphatic system, genitourinary tract (including bladder and prostate), ovarian, gastric, bone, or pancreatic tumors, using the compounds of the present invention, methods of their administration, methods of their formulation, and methods of their synthesis.

The compounds of the present invention are additionally useful in the treatment of one or more diseases afflicting mammals which are characterized by cellular proliferation in the areas of blood vessel proliferative disorders, fibrotic disorders, mesangial cell proliferative disorders and metabolic diseases. Blood vessel proliferative disorders include arthritis and restenosis. Fibrotic disorders include hepatic cirrhosis and atherosclerosis. Mesangial cell proliferative disorders include glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, organ transplant rejection and glomerulopathies. Metabolic disorders include psoriasis, diabetes mellitus, chronic wound healing, inflammation and neurodegenerative diseases.

SUMMARY OF THE INVENTION

In summary, the invention includes a family of compounds having the general structural formula (I):



wherein:

R¹ is Het, aryl, or biaryl with said Het, aryl, or biaryl being optionally substituted by one to four substituents selected from the group consisting of R⁵, C(O)R⁵, C(O)OR⁵, and OR⁵, where Het and R⁵ are as defined below;

5 R² is H, Het, fused Het, aryl, C₁₋₁₂ aliphatic, -CN, -NO₂, halogen, -OR⁵, -SR⁵,
 -S(O)R⁵, -NR⁵R⁷, -NR⁵COR⁵, -NR⁵CO₂R⁵, -NR⁵CONR⁵R⁷, -NR⁵SO₂R⁵,
 -NR⁵C(NR⁵)NHR⁵, -COR⁵, -CO₂R⁵, -CONR⁵R⁷, -SO₂NR⁵R⁷,
 -OCONR⁵R⁷, or -C(NR⁵)NR⁵R⁷, where said C₁₋₁₂ aliphatic optionally bears
 one or two aliphatic chain insertions selected from the group consisting of
 10 -C(O)-, -O-, -S-, -S(O)-, -S(O₂)-, and -N(R⁵)-, and wherein said Het, fused Het,
 aryl or C₁₋₁₂ aliphatic are optionally substituted by one to three of R⁵, and
 where Het, fused Het, R⁵ and R⁷ are as defined below;

15 R³ is H, Het, fused Het, aryl, C₁₋₁₂ aliphatic, CN, NO₂, halogen, -OR⁵, -SR⁵,
 -S(O)R⁵, -NR⁵R⁷, -NR⁵COR⁵, -NR⁵CO₂R⁵, -NR⁵CONR⁵R⁷, -NR⁵SO₂R⁵,
 -NR⁵C(NR⁵)NHR⁵, -COR⁵, -CO₂R⁵, -CONR⁵R⁷, -SO₂NR⁵R⁷, aryl-
 SO₂NR⁵R⁷, -OCONR⁵R⁷, or -C(NR⁵)NR⁵R⁷, where said C₁₋₁₂ aliphatic
 optionally bears one to two aliphatic chain insertions selected from the group
 consisting of
 20 -C(O)-, -O-, -S-, -S(O)-, -S(O₂)-, and -N(R⁵)-, where said Het, aryl or C₁₋₁₂
 aliphatic are optionally substituted by one to three of R⁵, and where Het, fused
 Het, R⁵ and R⁷ are as defined below;

25 R⁴ is H, Het, fused Het, aryl, C₁₋₁₂ aliphatic, -CN, -NO₂, halogen, -OR⁵, -SR⁵,
 -S(O)R⁵, -NR⁵R⁷, -NR⁵COR⁵, -NR⁵CO₂R⁵, -NR⁵CONR⁵R⁷, -NR⁵SO₂R⁵,
 -NR⁵C(NR⁵)NHR⁵, -COR⁵, -CO₂R⁵, -CONR⁵R⁷, -SO₂NR⁵R⁷,
 -OCONR⁵R⁷, or -C(NR⁵)NR⁵R⁷, where said C₁₋₁₂ aliphatic optionally bears
 one or two aliphatic chain insertions selected from the group consisting of
 -C(O)-, -O-, -S-, -S(O)-, -S(O₂)-, and -N(R⁵)-, and wherein said Het, fused Het,
 30 aryl or C₁₋₁₂ aliphatic are optionally substituted by one to three of R⁵, and
 where Het, fused Het, R⁵ and R⁷ are as defined below;

35 R⁵ is H, Het, aryl, halogen, or C₁₋₁₂ aliphatic, where said C₁₋₁₂ aliphatic
 optionally bears one to two aliphatic chain insertions selected from the group
 consisting of -O-, -S-, -S(O)-, -S(O₂)-, and -N(R⁶)-, where said C₁₋₁₂ aliphatic,

aryl, or Het is optionally substituted by one to four of halogen, another Het or substituted Het, aryl or substituted aryl, -CN, -NO₂, -R⁶, -SR⁶, -OR⁶, -N(R⁶)₂, -S(O)R⁶, -SO₂R⁶, -SO₂N(R⁶)₂, NR⁶COR⁶, -NR⁶CON(R⁶)₂, -NR⁶(NR⁶)NHR⁶, -CO₂R⁶, -CON(R⁶)₂,

-NR⁶SO₂R⁶, -OCON(R⁶)₂, or -NR⁶CO₂R⁶, where substituted Het and substituted aryl bear substituents that are any of -CN, -NO₂, -R⁶, -SR⁶, -OR⁶, -N(R⁶)₂, -S(O)R⁶, -SO₂R⁶, -SO₂N(R⁶)₂, NR⁶COR⁶, -NR⁶CON(R⁶)₂, -NR⁶(NR⁶)NHR⁶, -CO₂R⁶, -CON(R⁶)₂, -NR⁶SO₂R⁶, -OCON(R⁶)₂, or -NR⁶CO₂R⁶ and where Het and R⁶ are as defined below;

R⁶ is H, C₁₋₁₂ aliphatic, Het or aryl, where said C₁₋₁₂ aliphatic, Het or aryl is optionally substituted by one to three of halogen or OH, and where Het is as defined below;

R⁷ is H or R⁵;

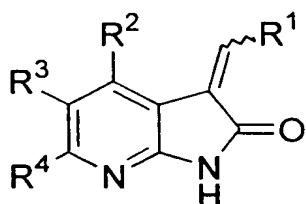
Het is a five to ten membered saturated or unsaturated heterocyclic ring selected from the group consisting of acridine, benzimidazole, benzofuran, benzothiophene, benzoxazole, benzthiazole, carbazole, cinnoline, dioxin, dioxane, dioxalane, dithiane, dithiazine, dithiazole, dithiolane, furan, imidazole, imidazoline, imidazolidine, indole, indoline, indolizine, indazole, isoindole, isoquinoline, isoxazole, isothiazole, morpholine, naphthyridine, oxazole, oxadiazole, oxathiazole, oxathiazolidine, oxazine, oxadiazine, phenazine, phenothiazine, phenoxazine, phthalazine, piperazine, piperidine, pteridine, purine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrroline, quinoline, quinoxaline, quinazoline, quinolizine, tetrahydrofuran, tetrazine, tetrazole, thiophene, thiadiazine, thiadiazole, thiatriazole, thiazine, thiazole, thiomorpholine, thianaphthalene, thiopyran, triazine, triazole, and trithiane;

fused Het is where R² and R³ or where R³ and R⁴ are optionally joined to form a fused ring selected from the group consisting of 5-10 membered aryl rings, 5-10 membered saturated heteroaryl rings or 5-10 membered unsaturated heterocyclyl rings, said heteroaryl or said heterocyclyl rings having one to three heteroatoms where zero to three of said heteroatoms are N and zero to

one of said heteroatoms are O or S and where said fused ring is optionally substituted by one to three of R^5 , where R^5 is defined above;

and the pharmaceutically acceptable salts, biohydrolyzable esters, biohydrolyzable amides, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, solvates, hydrates, affinity reagents or prodrugs of (I) as defined above.

A preferred group of compounds of the present invention are those of the structural formula



(I)

wherein:

R^1 is Het, aryl, or biaryl with said Het, aryl, or biaryl being optionally substituted by one to four substituents selected from the group consisting of R^5 , $C(O)R^5$, $C(O)OR^5$, and OR^5 , where Het and R^5 are as defined below;

R^2 is H, Het, fused Het, aryl, C_{1-6} aliphatic, -CN, -NO₂, halogen, -OR⁵, -SR⁵, -S(O)R⁵, -NR⁵R⁷, -NR⁵COR⁵, -NR⁵CO₂R⁵, -NR⁵CONR⁵R⁷, -NR⁵SO₂R⁵, -NR⁵C(NR⁵)NHR⁵, -COR⁵, -CO₂R⁵, -CONR⁵R⁷, -SO₂NR⁵R⁷, -OCONR⁵R⁷, or -C(NR⁵)NR⁵R⁷, where said C_{1-6} aliphatic optionally bears one or two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, -S(O₂)-, and -N(R⁵)-, and wherein said Het, fused Het, aryl or C_{1-6} aliphatic are optionally substituted by one to three of R^5 , and where Het, fused Het, R^5 and R^7 are as defined below;

R^3 is H, Het, fused Het, aryl, C_{1-6} aliphatic, CN, NO₂, halogen, -OR⁵, -SR⁵,

-S(O)R⁵, -NR⁵R⁷, -NR⁵COR⁵, -NR⁵CO₂R⁵, -NR⁵CONR⁵R⁷, -NR⁵SO₂R⁵,
 -NR⁵C(NR⁵)NHR⁵, -COR⁵, -CO₂R⁵, -CONR⁵R⁷, -SO₂NR⁵R⁷,
 aryl-SO₂NR⁵R⁷, -OCONR⁵R⁷, or -C(NR⁵)NR⁵R⁷, where said C₁₋₆ aliphatic
 optionally bears one to two aliphatic chain insertions selected from the group
 consisting of

-C(O)-, -O-, -S-, -S(O)-, -S(O₂)-, and -N(R⁵)-, where said Het, aryl or C₁₋₆
 aliphatic are optionally substituted by one to three of R⁵, and where Het, fused
 Het, R⁵ and R⁷ are as defined below;

R⁴ is H, Het, fused Het, aryl, C₁₋₆ aliphatic, -CN, -NO₂, halogen, -OR⁵, -SR⁵,
 -S(O)R⁵, -NR⁵R⁷, -NR⁵COR⁵, -NR⁵CO₂R⁵, -NR⁵CONR⁵R⁷, -NR⁵SO₂R⁵,
 -NR⁵C(NR⁵)NHR⁵,
 -COR⁵, -CO₂R⁵, -CONR⁵R⁷, -SO₂NR⁵R⁷, -OCONR⁵R⁷, or -C(NR⁵)NR⁵R⁷,
 where said C₁₋₆ aliphatic optionally bears one or two aliphatic chain insertions
 selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, -S(O₂)-, and
 -N(R⁵)-, and wherein said Het, fused Het, aryl or C₁₋₆ aliphatic are optionally
 substituted by one to three of R⁵, and where Het, fused Het, R⁵ and R⁷ are as
 defined below;

R⁵ is H, Het, aryl, halogen, or C₁₋₆ aliphatic, where said C₁₋₆ aliphatic optionally
 bears one to two aliphatic chain insertions selected from the group consisting
 of -O-, -S-, -S(O)-, -S(O₂)-, and -N(R⁶)-, where said C₁₋₆ aliphatic, aryl, or Het
 is optionally substituted by one to four of halogen, another Het or substituted
 Het, aryl or substituted aryl, -CN, -NO₂, -R⁶, -SR⁶, -OR⁶, -N(R⁶)₂, -S(O)R⁶,
 -SO₂R⁶, -SO₂N(R⁶)₂, NR⁶COR⁶, -NR⁶CON(R⁶)₂, -NR⁶(NR⁶)NHR⁶, -CO₂R⁶,
 -CON(R⁶)₂, -NR⁶SO₂R⁶, -OCON(R⁶)₂, or -NR⁶CO₂R⁶, where substituted Het
 and substituted aryl bear substituents that are any of -CN, -NO₂, -R⁶, -SR⁶,
 -OR⁶, -N(R⁶)₂, -S(O)R⁶, -SO₂R⁶, -SO₂N(R⁶)₂, NR⁶COR⁶, -NR⁶CON(R⁶)₂,
 -NR⁶(NR⁶)NHR⁶, -CO₂R⁶, -CON(R⁶)₂, -NR⁶SO₂R⁶, -OCON(R⁶)₂, or
 -NR⁶CO₂R⁶ and where Het and R⁶ are as defined below;

R⁶ is H, C₁₋₆ aliphatic, Het or aryl, where said C₁₋₁₂ aliphatic, Het or aryl is
 optionally substituted by one to three of halogen or OH, and where Het is as
 defined below;

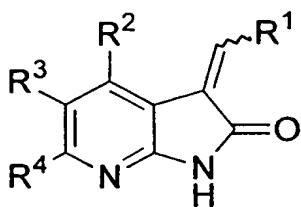
R^7 is H or R^5 ;

Het is a five to ten membered saturated or unsaturated heterocyclic ring selected from the group consisting of acridine, benzimidazole, benzofuran, benzothiophene, benzoxazole, benzthiazole, carbazole, cinnoline, dioxin, dioxane, dioxalane, dithiane, dithiazine, dithiazole, dithiolane, furan, imidazole, imidazoline, imidazolidine, indole, indoline, indolizine, indazole, isoindole, isoquinoline, isoxazole, isothiazole, morpholine, naphthyridine, oxazole, oxadiazole, oxathiazole, oxathiazolidine, oxazine, oxadiazine, phenazine, phenothiazine, phenoxazine, phthalazine, piperazine, piperidine, pteridine, purine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrroline, quinoline, quinoxaline, quinazoline, quinolizine, tetrahydrofuran, tetrazine, tetrazole, thiophene, thiadiazine, thiadiazole, thiatriazole, thiazine, thiazole, thiomorpholine, thianaphthalene, thiopyran, triazine, triazole, and trithiane;

fused Het is where R^2 and R^3 or where R^3 and R^4 are optionally joined to form a fused ring selected from the group consisting of 5-10 membered aryl rings, 5-10 membered saturated heteroaryl rings or 5-10 membered unsaturated heterocyclyl rings, said heteroaryl or said heterocyclyl rings having one to three heteratoms where zero to three of said heteroatoms are N and zero to one of said heteroatoms are O or S and where said fused ring is optionally substituted by one to three of R^5 , where R^5 is defined above;

and the pharmaceutically acceptable salts, biohydrolyzable esters, biohydrolyzable amides, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, solvates, hydrates, affinity reagents or prodrugs of (I) as defined above.

A highly preferred group of compounds of the present invention are those of the general formula (I)



(I)

5 wherein:

10 R¹ is Het or aryl, with said Het or aryl optionally substituted by one to four substituents selected from the group consisting of C₁₋₆ lower alkyl, halogen, -(CH₂)₁₋₆ OH, -O(CH₂)₃N(CH₃)₂, -NO₂, -OR⁵, -NH(CO)CH₃, -C(O)R⁵, aryloxy, -C₆H₅SO₂NH₂, or -C(O)OR⁵, where Het and R⁵ are as defined below;

15 R² is H;

20 R³ is Het, Het-R⁵, aryl, C₁₋₁₂ aliphatic, -COR⁵, -CO₂R⁵, or halogen, and where Het and R⁵ are as defined below;

25 R⁴ is H;

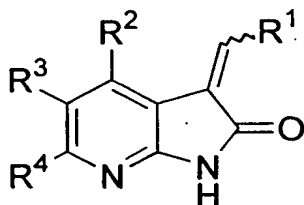
30 R⁵ is H, C₁₋₁₂ aliphatic, -SO₂R⁶, or -N(R⁶)₂, where said C₁₋₁₂ aliphatic is optionally substituted by one to four of halogen, where R⁶ is as defined below;

35 R⁶ is H, or NH₂;

40 Het is a five to ten membered saturated or unsaturated heterocyclic ring selected from the group consisting of pyridine, pyrrole, furan, quinoline, thiophene and thiazole,

45 and the pharmaceutically acceptable salts, biohydrolyzable esters, biohydrolyzable amides, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, solvates, hydrates, affinity reagents or prodrugs of (I) as defined above.

A group of compounds that are preferred with respect to their substituents at R^1 are compounds of the formula:



(I)

wherein:

R^1 is substituted phenyl, Het, or substituted Het, where said phenyl substituent is independently one or more of halogen, C_{1-6} lower alkyl, -OH, C_{1-6} lower alkyl-OH, C_{1-6} alkoxy, -O- C_6H_5 , C_{1-6} alkoxy substituted by amine, or amide substituted by C_{1-6} lower alkyl, and where said Het substituent is independently one or more of - CH_3 , or - $C_6H_5-SO_2NH_2$;

R^2 is H, Het, fused Het, aryl, C_{1-12} aliphatic, -CN, - NO_2 , halogen, - OR^5 , - SR^5 , - $S(O)R^5$, - NR^5R^7 , - NR^5COR^5 , - $NR^5CO_2R^5$, - $NR^5CONR^5R^7$, - $NR^5SO_2R^5$, - $NR^5C(NR^5)NHR^5$, - COR^5 , - CO_2R^5 , - $CONR^5R^7$, - $SO_2NR^5R^7$, - $OCONR^5R^7$, or - $C(NR^5)NR^5R^7$, where said C_{1-12} aliphatic optionally bears one or two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, -S(O_2)-, and -N(R^5)-, and wherein said Het, fused Het, aryl or C_{1-12} aliphatic are optionally substituted by one to three of R^5 , and where Het, fused Het, R^5 and R^7 are as defined below;

R^3 is H, Het, fused Het, aryl, C_{1-12} aliphatic, CN, NO_2 , halogen, - OR^5 , - SR^5 , - $S(O)R^5$, - NR^5R^7 , - NR^5COR^5 , - $NR^5CO_2R^5$, - $NR^5CONR^5R^7$, - $NR^5SO_2R^5$, - $NR^5C(NR^5)NHR^5$, - COR^5 , - CO_2R^5 , - $CONR^5R^7$, - $SO_2NR^5R^7$, aryl- $SO_2NR^5R^7$, - $OCONR^5R^7$, or - $C(NR^5)NR^5R^7$, where said C_{1-12} aliphatic optionally bears one to two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, -S(O_2)-, and -N(R^5)-, where said Het, aryl

or C₁₋₁₂ aliphatic are optionally substituted by one to three of R⁵, and where Het, fused Het, R⁵ and R⁷ are as defined below;

R⁴ is H, Het, fused Het, aryl, C₁₋₁₂ aliphatic, -CN, -NO₂, halogen, -OR⁵, -SR⁵,
 5 -S(O)R⁵, -NR⁵R⁷, -NR⁵COR⁵, -NR⁵CO₂R⁵, -NR⁵CONR⁵R⁷, -NR⁵SO₂R⁵,
 -NR⁵C(NR⁵)NHR⁵, -COR⁵, -CO₂R⁵, -CONR⁵R⁷, -SO₂NR⁵R⁷, -OCONR⁵R⁷,
 or -C(NR⁵)NR⁵R⁷, where said C₁₋₁₂ aliphatic optionally bears one or two
 aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-,
 -S(O)-, -S(O₂)-, and -N(R⁵)-, and wherein said Het, fused Het, aryl or C₁₋₁₂
 10 aliphatic are optionally substituted by one to three of R⁵, and where Het, fused
 Het, R⁵ and R⁷ are as defined below;

R⁵ is H, Het, aryl, halogen, or C₁₋₁₂ aliphatic, where said C₁₋₁₂ aliphatic
 15 optionally bears one to two aliphatic chain insertions selected from the group
 consisting of -O-, -S-, -S(O)-, -S(O₂)-, and -N(R⁶)-, where said C₁₋₁₂ aliphatic,
 aryl, or Het is optionally substituted by one to four of halogen, another Het or
 substituted Het, aryl or substituted aryl, -CN, -NO₂, -R⁶, -SR⁶, -OR⁶, -N(R⁶)₂,
 -S(O)R⁶, -SO₂R⁶, -SO₂N(R⁶)₂, NR⁶COR⁶, -NR⁶CON(R⁶)₂, -NR⁶(NR⁶)NHR⁶,
 -CO₂R⁶, -CON(R⁶)₂, -NR⁶SO₂R⁶, -OCON(R⁶)₂, or -NR⁶CO₂R⁶, where
 20 substituted Het and substituted aryl are any of -CN, -NO₂, -R⁶, -SR⁶, -OR⁶,
 -N(R⁶)₂, -S(O)R⁶, -SO₂R⁶, -SO₂N(R⁶)₂, NR⁶COR⁶, -NR⁶CON(R⁶)₂,
 -NR⁶(NR⁶)NHR⁶, -CO₂R⁶, -CON(R⁶)₂, -NR⁶SO₂R⁶, -OCON(R⁶)₂, or
 -NR⁶CO₂R⁶ and where Het and R⁶ are as defined below;

R⁶ is H, C₁₋₁₂ aliphatic, Het or aryl, where said C₁₋₁₂ aliphatic, Het or aryl is
 25 optionally substituted by one to three of halogen or OH, and where Het is as
 defined below;

R⁷ is H or R⁵;

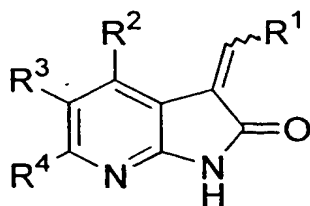
Het is a five to ten membered saturated or unsaturated heterocyclic ring
 selected from the group consisting of acridine, benzimidazole, benzofuran,
 benzothiophene, benzoxazole, benzthiazole, carbazole, cinnoline, dioxin,
 dioxane, dioxalane, dithiane, dithiazine, dithiazole, dithiolane, furan, imidazole,
 35 imidazoline, imidazolidine, indole, indoline, indolizine, indazole, isoindole,

isoquinoline, isoxazole, isothiazole, morpholine, naphthyridine, oxazole, oxadiazole, oxathiazole, oxathiazolidine, oxazine, oxadiazine, phenazine, phenothiazine, phenoxazine, phthalazine, piperazine, piperidine, pteridine, purine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrroline, quinoline, quinoxaline, quinazoline, quinolizine, tetrahydrofuran, tetrazine, tetrazole, thiophene, thiadiazine, thiadiazole, thiatriazole, thiazine, thiazole, thiomorpholine, thianaphthalene, thiopyran, triazine, triazole, and trithiane;

fused Het is where R^2 and R^3 or where R^3 and R^4 are optionally joined to form a fused ring selected from the group consisting of 5-10 membered aryl rings, 5-10 membered saturated heteroaryl rings or 5-10 membered unsaturated heterocyclyl rings, said heteroaryl or said heterocyclyl rings having one to three heteratoms where zero to three of said heteratoms are N and zero to one of said heteratoms are O or S and where said fused ring is optionally substituted by one to three of R^5 , where R^5 is defined above;

and the pharmaceutically acceptable salts, biohydrolyzable esters, biohydrolyzable amides, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, solvates, hydrates, affinity reagents or prodrugs of (I) as defined above.

Another group of compounds that are preferred with respect to their substituents at Position R^1 are compounds of the structural formula



(I)

wherein:

R^1 is substituted phenyl, Het, or substituted Het, where said phenyl substituent is independently one or more of halogen, C_{1-6} lower alkyl, -OH, C_{1-6} lower alkyl-OH, C_{1-6} alkoxy, -O- C_6H_5 , C_{1-6} alkoxy substituted by amine, or amide substituted by C_{1-6} lower alkyl, and where said Het substituent is independently one or more of -CH₃, or -C₆H₅-SO₂NH₂ ;

R^2 is H, Het, fused Het, aryl, C_{1-6} aliphatic, -CN, -NO₂, halogen, -OR⁵, -SR⁵, -S(O)R⁵, -NR⁵R⁷, -NR⁵COR⁵, -NR⁵CO₂R⁵, -NR⁵CONR⁵R⁷, -NR⁵SO₂R⁵, -NR⁵C(NR⁵)NHR⁵, -COR⁵, -CO₂R⁵, -CONR⁵R⁷, -SO₂NR⁵R⁷, -OCONR⁵R⁷, or -C(NR⁵)NR⁵R⁷, where said C_{1-6} aliphatic optionally bears one or two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, -S(O₂)-, and -N(R⁵)-, and wherein said Het, fused Het, aryl or C_{1-6} aliphatic are optionally substituted by one to three of R⁵, and where Het, fused Het, R⁵ and R⁷ are as defined below;

R^3 is H, Het, fused Het, aryl, C_{1-6} aliphatic, CN, NO₂, halogen, -OR⁵, -SR⁵, -S(O)R⁵, -NR⁵R⁷, -NR⁵COR⁵, -NR⁵CO₂R⁵, -NR⁵CONR⁵R⁷, -NR⁵SO₂R⁵, -NR⁵C(NR⁵)NHR⁵, -COR⁵, -CO₂R⁵, -CONR⁵R⁷, -SO₂NR⁵R⁷, aryl-SO₂NR⁵R⁷, -OCONR⁵R⁷, or -C(NR⁵)NR⁵R⁷, where said C_{1-6} aliphatic optionally bears one to two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, -S(O₂)-, and -N(R⁵)-, where said Het, aryl or C_{1-6} aliphatic are optionally substituted by one to three of R⁵, and where Het, fused Het, R⁵ and R⁷ are as defined below;

R^4 is H, Het, fused Het, aryl, C_{1-6} aliphatic, -CN, -NO₂, halogen, -OR⁵, -SR⁵, -S(O)R⁵, -NR⁵R⁷, -NR⁵COR⁵, -NR⁵CO₂R⁵, -NR⁵CONR⁵R⁷, -NR⁵SO₂R⁵, -NR⁵C(NR⁵)NHR⁵, -COR⁵, -CO₂R⁵, -CONR⁵R⁷, -SO₂NR⁵R⁷, -OCONR⁵R⁷, or -C(NR⁵)NR⁵R⁷, where said C_{1-6} aliphatic optionally bears one or two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, -S(O₂)-, and -N(R⁵)-, and wherein said Het, fused Het, aryl or C_{1-6} aliphatic are optionally substituted by one to three of R⁵, and where Het, fused Het, R⁵ and R⁷ are as defined below;

R^5 is H, Het, aryl, halogen, or C_{1-6} aliphatic, where said C_{1-6} aliphatic optionally bears one to two aliphatic chain insertions selected from the group consisting of -O-, -S-, -S(O)-, -S(O₂)-, and -N(R^6)-, where said C_{1-6} aliphatic, aryl, or Het is optionally substituted by one to four of halogen, another Het or substituted Het, aryl or substituted aryl, -CN, -NO₂, - R^6 , -SR⁶, -OR⁶, -N(R^6)₂, -S(O)R⁶, -SO₂R⁶, -SO₂N(R^6)₂, NR⁶COR⁶, -NR⁶CON(R^6)₂, -NR⁶(NR⁶)NHR⁶, -CO₂R⁶, -CON(R^6)₂, -NR⁶SO₂R⁶, -OCON(R^6)₂, or -NR⁶CO₂R⁶, where substituted Het and substituted aryl are any of -CN, -NO₂, - R^6 , -SR⁶, -OR⁶, -N(R^6)₂, -S(O)R⁶, -SO₂R⁶, -SO₂N(R^6)₂, NR⁶COR⁶, -NR⁶CON(R^6)₂, -NR⁶(NR⁶)NHR⁶, -CO₂R⁶, -CON(R^6)₂, -NR⁶SO₂R⁶, -OCON(R^6)₂, or -NR⁶CO₂R⁶ and where Het and R^6 are as defined below;

R^6 is H, C_{1-6} aliphatic, Het or aryl, where said C_{1-12} aliphatic, Het or aryl is optionally substituted by one to three of halogen or OH, and where Het is as defined below;

R^7 is H or R^5 ;

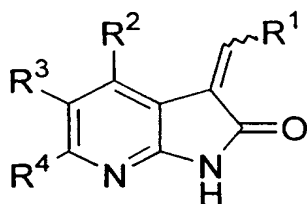
Het is a five to ten membered saturated or unsaturated heterocyclic ring selected from the group consisting of acridine, benzimidazole, benzofuran, benzothiophene, benzoxazole, benzthiazole, carbazole, cinnoline, dioxin, dioxane, dioxalane, dithiane, dithiazine, dithiazole, dithiolane, furan, imidazole, imidazoline, imidazolidine, indole, indoline, indolizine, indazole, isoindole, isoquinoline, isoxazole, isothiazole, morpholine, naphthyridine, oxazole, oxadiazole, oxathiazole, oxathiazolidine, oxazine, oxadiazine, phenazine, phenothiazine, phenoxazine, phthalazine, piperazine, piperidine, pteridine, purine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrroline, quinoline, quinoxaline, quinazoline, quinolizine, tetrahydrofuran, tetrazine, tetrazole, thiophene, thiadiazine, thiadiazole, thiatriazole, thiazine, thiazole, thiomorpholine, thianaphthalene, thiopyran, triazine, triazole, and trithiane;

fused Het is where R^2 and R^3 or where R^3 and R^4 are optionally joined to form a fused ring selected from the group consisting of 5-10 membered aryl rings, 5-10 membered saturated heteroaryl rings or 5-10 membered unsaturated

heterocyclyl rings, said heteroaryl or said heterocyclyl rings having one to three heteratoms where zero to three of said heteratoms are N and zero to one of said heteratoms are O or S and where said fused ring is optionally substituted by one to three of R^5 , where R^5 is defined above;

and the pharmaceutically acceptable salts, biohydrolyzable esters, biohydrolyzable amides, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, solvates, hydrates, affinity reagents or prodrugs of (I) as defined above.

Yet another group of compounds that are preferred with respect to their substituents at position R^1 are compounds of the structural formula



(I)

wherein:

R^1 is substituted phenyl, Het, or substituted Het, where said phenyl substituent is independently one or more of halogen, C_{1-6} lower alkyl, $-OH$, C_{1-6} lower alkyl- OH , C_{1-6} alkoxy, $-O-C_6H_5$, C_{1-6} alkoxy substituted by amine, or amide substituted by C_{1-6} lower alkyl, and where said Het substituent is independently one or more of $-CH_3$, or $-C_6H_5-SO_2NH_2$;

R^2 is H;

R^3 is Het, Het- R^5 , aryl, C_{1-12} aliphatic, $-COR^5$, $-CO_2R^5$, or halogen, and where Het and R^5 are as defined below;

R^4 is H;

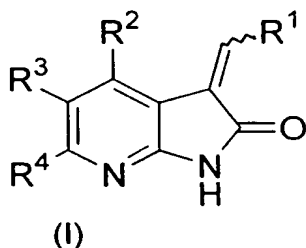
R^5 is H, C_{1-12} aliphatic, $-SO_2R^6$, or $-N(R^6)_2$, where said C_{1-12} aliphatic is optionally substituted by one to four of halogen, where R^6 is as defined below;

R^6 is H, or NH_2 ;

Het is a five to ten membered saturated or unsaturated heterocyclic ring selected from the group consisting of pyridine, pyrrole, furan, quinoline, thiophene and thiazole,

and the pharmaceutically acceptable salts, biohydrolyzable esters, biohydrolyzable amides, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, solvates, hydrates, affinity reagents or prodrugs of (I) as defined above.

Still another group of compounds that are preferred with respect to their substituents at position R^1 are compounds of the structural formula



wherein:

R^1 is phenyl, substituted phenyl, Het, or substituted Het, where said phenyl substituent is independently one or more of Br, F, -OH, $-CH_2OH$, $-O-CH_3$, $-O-C_6H_5$, $-O-(CH_2)_3NH_2$, $-C(CH_3)_2$, or $-NHCOCH_3$, and where said Het substituent is independently one or more of $-CH_3$, or $-C_6H_5-SO_2NH_2$.

R^2 is H, Het, fused Het, aryl, C_{1-12} aliphatic, -CN, $-NO_2$, halogen, $-OR^5$, $-SR^5$, $-S(O)R^5$, $-NR^5R^7$, $-NR^5COR^5$, $-NR^5CO_2R^5$, $-NR^5CONR^5R^7$, $-NR^5SO_2R^5$, $-NR^5C(NR^5)NHR^5$, $-COR^5$, $-CO_2R^5$, $-CONR^5R^7$, $-SO_2NR^5R^7$,

-OCONR⁵R⁷, or -C(NR⁵)NR⁵R⁷, where said C₁₋₁₂ aliphatic optionally bears one or two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, -S(O₂)-, and -N(R⁵)-, and wherein said Het, fused Het, aryl or C₁₋₁₂ aliphatic are optionally substituted by one to three of R⁵, and where Het, fused Het, R⁵ and R⁷ are as defined below;

R³ is H, Het, fused Het, aryl, C₁₋₁₂ aliphatic, CN, NO₂, halogen, -OR⁵, -SR⁵, -S(O)R⁵, -NR⁵R⁷, -NR⁵COR⁵, -NR⁵CO₂R⁵, -NR⁵CONR⁵R⁷, -NR⁵SO₂R⁵, -NR⁵C(NR⁵)NHR⁵, -COR⁵, -CO₂R⁵, -CONR⁵R⁷, -SO₂NR⁵R⁷, aryl-SO₂NR⁵R⁷, -OCONR⁵R⁷, or -C(NR⁵)NR⁵R⁷, where said C₁₋₁₂ aliphatic optionally bears one to two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, -S(O₂)-, and -N(R⁵)-, where said Het, aryl or C₁₋₁₂ aliphatic are optionally substituted by one to three of R⁵, and where Het, fused Het, R⁵ and R⁷ are as defined below;

R⁴ is H, Het, fused Het, aryl, C₁₋₁₂ aliphatic, -CN, -NO₂, halogen, -OR⁵, -SR⁵, -S(O)R⁵, -NR⁵R⁷, -NR⁵COR⁵, -NR⁵CO₂R⁵, -NR⁵CONR⁵R⁷, -NR⁵SO₂R⁵, -NR⁵C(NR⁵)NHR⁵, -COR⁵, -CO₂R⁵, -CONR⁵R⁷, -SO₂NR⁵R⁷, -OCONR⁵R⁷, or -C(NR⁵)NR⁵R⁷, where said C₁₋₁₂ aliphatic optionally bears one or two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, -S(O₂)-, and -N(R⁵)-, and wherein said Het, fused Het, aryl or C₁₋₁₂ aliphatic are optionally substituted by one to three of R⁵, and where Het, fused Het, R⁵ and R⁷ are as defined below;

R⁵ is H, Het, aryl, halogen, or C₁₋₁₂ aliphatic, where said C₁₋₁₂ aliphatic optionally bears one to two aliphatic chain insertions selected from the group consisting of -O-, -S-, -S(O)-, -S(O₂)-, and -N(R⁶)-, where said C₁₋₁₂ aliphatic, aryl, or Het is optionally substituted by one to four of halogen, another Het or substituted Het, aryl or substituted aryl, -CN, -NO₂, -R⁶, -SR⁶, -OR⁶, -N(R⁶)₂, -S(O)R⁶, -SO₂R⁶, -SO₂N(R⁶)₂, NR⁶COR⁶, -NR⁶CON(R⁶)₂, -NR⁶(NR⁶)NHR⁶, -CO₂R⁶, -CON(R⁶)₂, -NR⁶SO₂R⁶, -OCON(R⁶)₂, or -NR⁶CO₂R⁶, where substituted Het and substituted aryl are any of -CN, -NO₂, -R⁶, -SR⁶, -OR⁶, -N(R⁶)₂, -S(O)R⁶, -SO₂R⁶, -SO₂N(R⁶)₂, NR⁶COR⁶, -NR⁶CON(R⁶)₂, -NR⁶(NR⁶)NHR⁶, -CO₂R⁶, -CON(R⁶)₂,

-NR⁶SO₂R⁶, -OCON(R⁶)₂, or -NR⁶CO₂R⁶ and where Het and R⁶ are as defined below;

5 R⁶ is H, C₁₋₁₂ aliphatic, Het or aryl, where said C₁₋₁₂ aliphatic, Het or aryl is optionally substituted by one to three of halogen or OH, and where Het is as defined below;

R⁷ is H or R⁵;

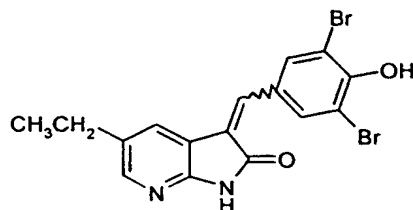
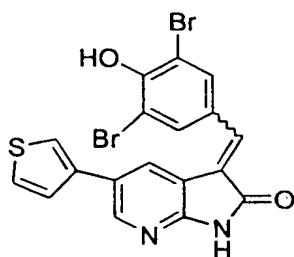
10 Het is a five to ten membered saturated or unsaturated heterocyclic ring selected from the group consisting of pyrrole, furan, thiophene, pyrazole, or indole;

15 fused Het is where R² and R³ or where R³ and R⁴ are optionally joined to form a fused ring selected from the group consisting of 5-10 membered aryl rings, 5-10 membered saturated heteroaryl rings or 5-10 membered unsaturated heterocyclyl rings, said heteroaryl or said heterocyclyl rings having one to three heteratoms where zero to three of said heteroatoms are N and zero to one of said heteroatoms are O or S and where said fused ring is optionally
20 substituted by one to three of R⁵, where R⁵ is defined above;

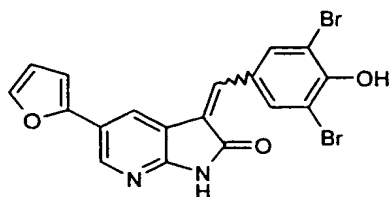
25 and the pharmaceutically acceptable salts, biohydrolyzable esters, biohydrolyzable amides, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, solvates, hydrates, affinity reagents or prodrugs of (I) as defined above.

A preferred sub-group of compounds includes those of the following structural formula:

21

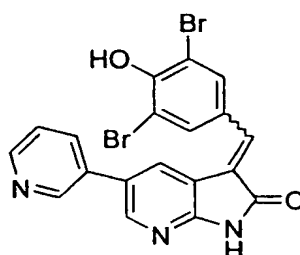
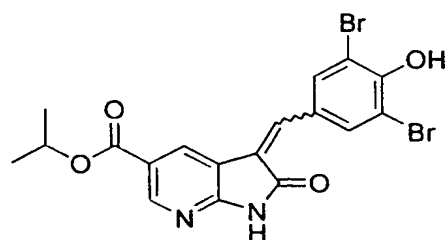
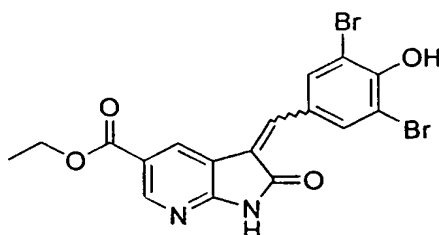
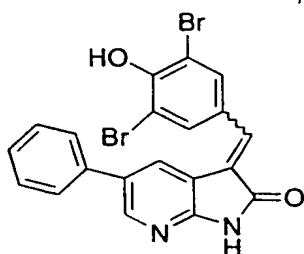
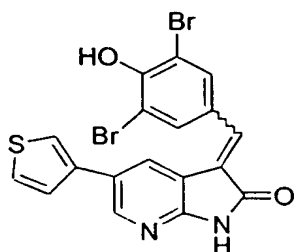


and



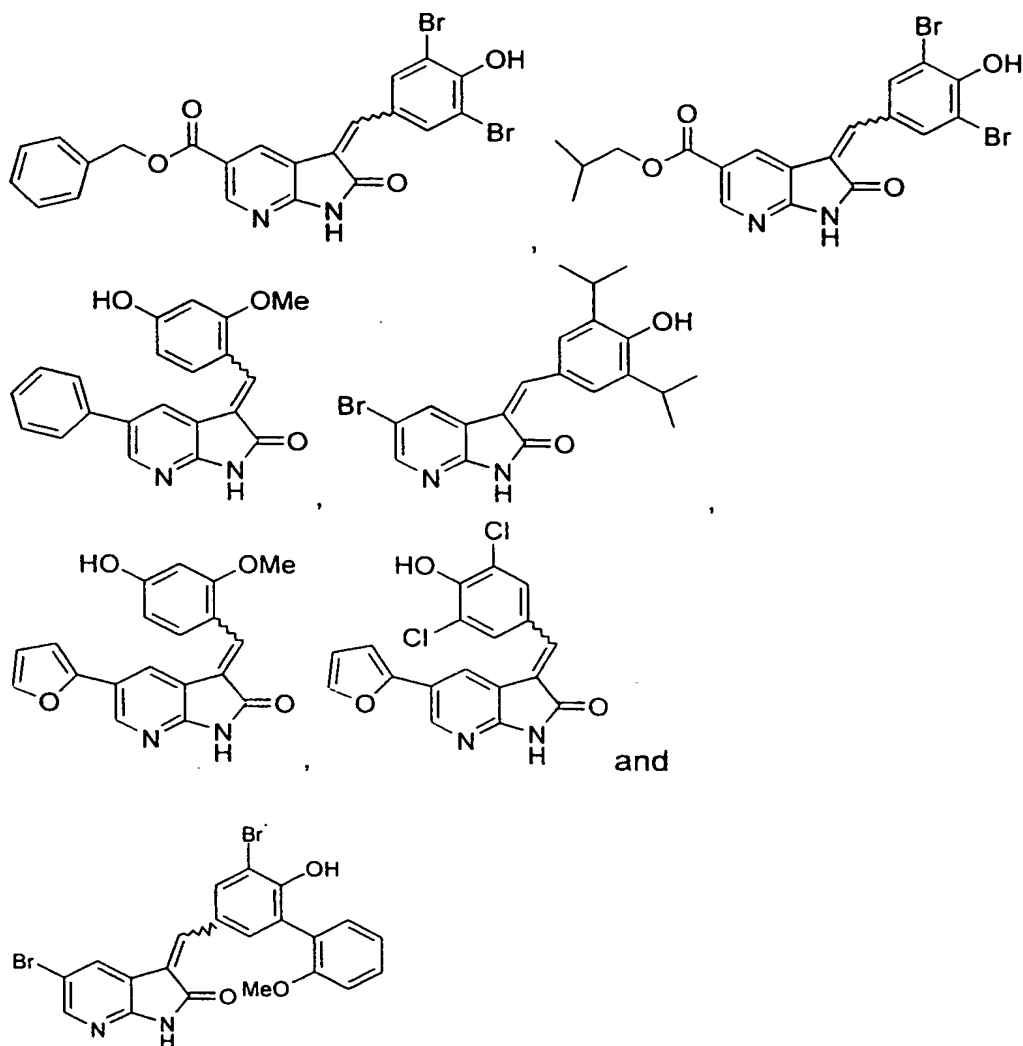
Another preferred sub-group of compounds includes those of the following structural formula:

5



10

22



5

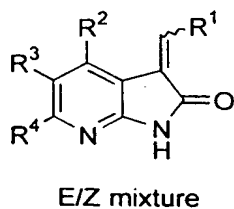
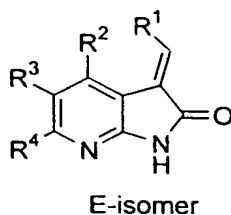
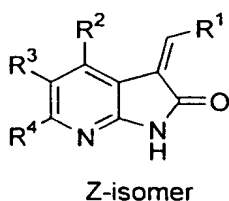
Certain compounds of formula (I) above may exist in stereoisomeric forms (e.g. they may contain one or more asymmetric carbon atoms or may exhibit cis-trans isomerism). The individual stereoisomers (enantiomers and diastereoisomers) and mixtures of these are included within the scope of the present invention. Likewise, it is understood that compounds of formula (I) may exist in tautomeric forms other than that shown in the formula and these are also included within the scope of the present invention.

15

Due to the presence of a double bond, also included in the compounds of the invention are their respective pure E and Z geometric isomers as well as mixtures of E and Z isomers.

5 The invention as described and as claimed does not set any limiting ratios on prevalence of Z to E isomers.

10 Thus, compound 3-(3,5-Dibromo-4-hydroxy-benzylidene)-5-furan-2-yl-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one, (compound number 7 in the tables below), is disclosed and claimed as the E geometric isomer thereof, the Z geometric isomer and a mixture of the E and Z geometric isomers thereof, but not limited by any given ratio(s).



15 Certain of the compounds as described will contain one or more chiral atoms or chiral groups and therefore be either dextrorotary or levorotary. Also included in the compounds of the invention are the respective dextrorotary or levorotary pure preparations, and racemic mixtures thereof.

20 Salts of the compounds of the present invention may comprise acid addition salts derived from a nitrogen on a substituent in the compound of formula (I). The therapeutic activity of the invention resides in the moiety derived from the compound of the invention as defined herein and the identity of another component, such as a salt cation, is of less importance although for

25

therapeutic and prophylactic purposes it is, preferably, pharmaceutically acceptable to the patient.

Highly preferred biohydrolyzable carbamates comprise compounds of formula (I), wherein R¹ is phenyl substituted at the para- position by OH and said OH is conjugated with a carbamoyl conjugate to yield a biohydrolyzable carbamate wherein said carbamoyl conjugate is selected from the group consisting of diethylaminocarbonyl, N-(2-hydroxyethyl)aminocarbonyl, N,N,-bis(2-hydroxyethyl)aminocarbonyl, hydroxyethyloxyethylaminocarbonyl, 4-morpholinocarbonyl and 4-methyl-1-piperazinylcarbonyl.

Highly preferred biohydrolyzable carbonates comprise compounds of formula (I), wherein R¹ is phenyl substituted at the para- position by OH and said OH is conjugated with a carbonate conjugate to yield a biohydrolyzable carbonate wherein said carbonyl conjugate is selected from the group consisting of phenylmethyloxyxcarbonyl, ethyloxyxcarbonyl, isobutyloxyxcarbonyl, and pyridinemethyloxyxcarbonyl.

Highly preferred biohydrolyzable esters comprise compounds of formula (I), wherein R¹ is phenyl substituted at the para- position by OH and said OH is conjugated with an ester conjugate to yield a biohydrolyzable ester wherein said ester conjugate is selected from the group consisting of t-butylcarbonyloxymethyl.

Independent Substituents

The invention discloses four different points of substitution on structural formula (I). Each of these points of substitution bears a substituent whose selection and synthesis as part of this invention was independent of all other points of substitution on formula (I). Thus, each point of substitution is now further described individually.

R¹ is a selected heterocyclic ring, an aryl ring, or a biaryl ring. Any of these ring types can be optionally substituted by up to four substituents. These

substituents can be selected from among R^5 , which is defined further below; carbonyl- R^5 ; ester- R^5 ; and ether- R^5 .

5 R^1 is alternatively a selected heterocyclic ring, or an aryl ring, which can be substituted by up to four substituents selected from a group consisting of 1 to 6 carbon lower alkyl, halogen, 1-6 carbon lower alkyl substituted hydroxyl, nitro, ether- R^5 , carboxyl- R^5 , aryloxy, sulfonamide substituted phenyl, ether-alkyl substituted by amine, amide substituted by alkyl, or ester- R^5 . Suitable heterocyclic rings include pyridine, pyrrole, furan, quinoline, thiophene and
10 thiazole.

R^1 is preferably substituted phenyl, a heterocyclic ring, or a substituted heterocyclic ring. Suitable phenyl substituents include halogen, 1-6 carbon lower alkyl, hydroxy, 1-6 carbon lower alkyl hydroxy, 1-6 carbon lower alkoxy, phenoxy, 1-6 carbon lower alkoxy substituted by amine, or amide substituted by 1-6 carbon lower alkyl. Suitable heterocyclic ring substituents include methyl and sulfonamide phenyl.
15

Most preferably, R^1 is substituted phenyl or a substituted heterocyclic ring. Suitable phenyl substituents include one or more of bromine, fluorine, hydroxyl, hydroxymethyl, methoxy, phenoxy, aminopropoxy, isopropyl or methylamido. Suitable heterocyclic substituents include one or more of methyl or sulfonamide phenyl.
20

R^2 is a heterocyclic ring, a fused heterocyclic ring system, aryl, a 1-12 carbon aliphatic chain, cyano, nitro, halogen, ether- R^5 , thioether- R^5 , sulfonyl- R^5 , amine- R^5R^7 , amide- $(R^5)_{1-3}$, carbamate- $(R^5)_{1-2}$, ureate- $(R^5)_{1-2}$, sulfonamide- $(R^5)_{1-2}$, carbonyl- R^5 , ester- $(R^5)_{1-2}$, amide- R^5R^7 , or sulfonamide- R^5R^7 . The aliphatic chain can bear 1 to 2 insertions along its chain including oxygen, sulfur, sulfone, sulfone, carbonyl, or R^5 -substituted nitrogen. These aryl, heterocyclic and fused heterocyclic rings and these aliphatic chains can be substituted by 1 to 3 occurrences of R^5 .
25
30

More preferably, R^2 comprises aliphatic chains of 1 to 6 carbons.
35

Most preferably, R^2 is hydrogen.

R^3 is a heterocyclic ring, a fused heterocyclic ring system, aryl, a 1-12 carbon aliphatic chain, cyano, nitro, halogen, ether- R^5 , thioether- R^5 , sulphenyl- R^5 , amine- R^5R^7 , amide- $(R^5)_{1-3}$, carbamate- $(R^5)_{1-2}$, ureate- $(R^5)_{1-2}$, sulfonamide- $(R^5)_{1-2}$, carbonyl- R^5 , ester- $(R^5)_{1-3}$, amide- R^5R^7 , or sulfonamide- R^5R^7 . The aliphatic chain can bear 1 to 2 insertions along its chain including oxygen, sulfur, sulfine, sulfone, carbonyl, or R^5 -substituted nitrogen. These aryl, heterocyclic and fused heterocyclic rings and these aliphatic chains can be substituted by 1 to 3 occurrences of R^5 .

R^3 is more preferably an aryl ring, a heterocyclic ring, a substituted heterocyclic ring, a 1 to 12 carbon aliphatic chain, carbonyl- R^5 , ester- R^5 , or halogen.

R^4 is a heterocyclic ring, a fused heterocyclic ring system, aryl, a 1-12 carbon aliphatic chain, cyano, nitro, halogen, ether- R^5 , thioether- R^5 , sulphenyl- R^5 , amine- R^5R^7 , amide- $(R^5)_{1-3}$, carbamate- $(R^5)_{1-2}$, ureate- R^5 , sulfonamide- $(R^5)_{1-2}$, carbonyl- R^5 , ester- R^5 , amide- R^5R^7 , or sulfonamide- R^5R^7 . The aliphatic chain can bear 1 to 2 insertions along its chain including oxygen, sulfur, sulfine, sulfone, carbonyl, or R^5 -substituted nitrogen. These aryl, heterocyclic and fused heterocyclic rings and these aliphatic chains can be substituted by 1 to 3 occurrences of R^5 .

Most preferably, R^4 is hydrogen.

R^5 is hydrogen, a heterocyclic ring, an aryl ring, halogen, amino- R^6 or a 1-12 carbon aliphatic chain. The aliphatic chain can bear 1 to 2 insertions along its chain including oxygen, sulfur, sulfine, sulfone, carbonyl, or R^5 -substituted nitrogen. The heterocyclic ring, aryl ring or aliphatic chain can be substituted by from one to four of halogen, another heterocyclic ring or substituted heterocyclic ring, an aryl ring, a substituted aryl ring, cyano, nitro, R^6 , ether- R^6 , thioether- R^6 , amine- $(R^6)_{1-3}$, sulphenyl- R^6 , sulfonyl- R^6 , sulfonamide- $(R^6)_{1-2}$, ester- R^6 , amide- $(R^6)_{1-3}$, carbonate- $(R^6)_{1-2}$, carbamate- $(R^6)_{1-2}$. The aforesaid substituted heterocyclic or substituted aryl rings can likewise be substituted by

any of cyano, nitro, R^6 , ether- R^6 , thioether- R^6 , amine- $(R^6)_{1-3}$, sulfenyl- R^6 , sulfonyl- R^6 , sulfonamide- $(R^6)_{1-2}$, ester- R^6 , amide- $(R^6)_{1-3}$, carbonate- $(R^6)_{1-2}$, carbamate- $(R^6)_{1-2}$.

5 R^5 is more preferably hydrogen, 1-12 carbon aliphatic, sulfonyl- R^6 or amine- $(R^6)_2$. The aliphatic chain can be substituted by one to four occurrences of a halogen.

10 R^6 hydrogen, 1-12 carbon aliphatic, an aryl ring or a heterocyclic ring. The aryl or heterocyclic rings can be substituted by 1 to 3 occurrences of a halogen or a hydroxyl.

Preferably, R^6 is hydrogen or amine.

15 R^7 is hydrogen or R^5 .

Heterocyclic rings are suitably selected from the group of the following rings useful in medicinal chemistry: acridine, benzimidazole, benzofuran, benzothiophene, benzoxazole, benzthiazole, carbazole, cinnoline, dioxin, dioxane, dioxalane, dithiane, dithiazine, dithiazole, dithiolane, furan, imidazole, imidazoline, imidazolidine, indole, indoline, indolizine, indazole, isoindole, isoquinoline, isoxazole, isothiazole, morpholine, naphthyridine, oxazole, oxadiazole, oxathiazole, oxathiazolidine, oxazine, oxadiazine, phenazine, phenothiazine, phenoxazine, phthalazine, piperazine, piperidine, pteridine, purine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrroline, quinoline, quinoxaline, quinazoline, quinolizine, tetrahydrofuran, tetrazine, tetrazole, thiophene, thiadiazine, thiadiazole, thiatriazole, thiazine, thiazole, thiomorpholine, thianaphthalene, thiopyran, triazine, triazole, and trithiane.

30 Heterocyclic rings are more preferably selected from the group consisting of pyrrole, furan, thiophene, pyrazole, indole, pyridine or quinoline.

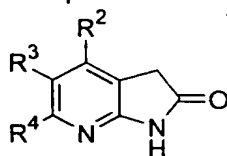
35 Fused heterocyclic ring systems include the structure where R^2 and R^3 or where R^3 and R^4 are optionally joined to form a fused ring selected from the

group consisting of 5-10 membered aryl rings, 5-10 membered saturated heteroaryl rings or 5-10 membered unsaturated heterocyclyl rings, said heteroaryl or said heterocyclyl rings having one to three heteroatoms where zero to three of said heteroatoms are N and zero to one of said heteroatoms are O or S and where said fused ring is optionally substituted by one to three of R⁵.

In a further aspect, the invention provides a process for the preparation of a compound of the formula (I), which process comprises the reaction of a compound of the formula (II)

R¹CHO (II)

with a compound of the formula (III)



(III), wherein all substituents are as defined above.

The reaction is conveniently carried out in the presence of a catalytic acid in the presence of a suitable inert solvent, for example an aromatic hydrocarbon or a halogenated hydrocarbon at a non-extreme temperature, for example from 0 °C to 150 °C, preferably 80 °C to 110 °C. Optionally the reaction is carried out in the presence of a strong acid, for example hydrochloric acid or sulfuric acid, in acetic acid as the solvent. Alternatively, the reaction may be carried out in the presence of a base, for example the treatment of (II) and (III) with a catalytic amount of piperidine in ethyl alcohol at temperatures between 22 °C and 78 °C.

The preparation of compounds (II) and (III) is known to those skilled in the art and many compounds having formula (II) are commercially available. (Jutz, Adv. Org. Chem., 9, 225-342, 1975; Truce, Org. React., 9, 37-72, 1957, Marfat, A.; Carta, M. P. Tetrahedron Letters 1987, 28, 4027 and references cited therein).

In addition to the above, one compound within the genus of formula (I) may be converted to another compound within the genus of formula (I) by chemical transformation of the appropriate substituent or substituents.

5 The compounds and salts of formula (I) have pharmacological activity as demonstrated hereinafter by their inhibition of protein kinase enzyme(s). It has thus been established that compounds of the present invention are of potential use in medicine. The present invention thus also provides
10 compounds of formula (I) and pharmaceutically acceptable salts, solvates, hydrates, affinity reagents or prodrugs, biohydrolyzable esters, amides, carbonates, amines, ureides or carbamates thereof (hereinafter identified as the 'active compounds') for use in medical therapy, and particularly in the treatment of disorders mediated by protein kinase activity such as human malignancies. The compounds are especially useful for the treatment of
15 disorders which are caused by mutated ras and upregulated tyrosine kinase signalling pathways such as breast, ovarian, colon, lung (including non-small cell lung), pancreatic, prostate, and gastric cancers.

20 According to a further aspect of the present invention there is provided a method of treating a disease mediated by a mitogen activated protein kinase, comprising the step of administering to a mammal in need thereof a pharmacologically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, biohydrolyzable ester, biohydrolyzable
25 amide, biohydrolyzable carbamate, biohydrolyzable carbonate, biohydrolyzable ureide, solvate, hydrate, affinity reagent or prodrug thereof.

According to a further aspect of the present invention there is provided a method of treating a disease mediated by a kinase selected from the group consisting of ab1, ATK, bcr-ab1, Blk, Brk, Btk, c-kit, c-met, c-src, CDK1,
30 CDK2, CDK4, CDK6, cRaf1, CSF1R, CSK, EGFR, ErbB2, ErbB3, ErbB4, ERK, Fak, fes, FGFR1, FGFR2, FGFR3, FGFR4, FGFR5, Fgr, FLK-4, flt-1, Fps, Frk, Fyn, GSK, Hck, IGF-1R, INS-R, Jak, JNK, KDR, Lck, Lyn, MEK, p38, PDGFR, PIK, PKC, PYK2, ros, tie₁, tie₂, TRK, UL97, Yes and Zap70, comprising the step of administering to a mammal in need thereof a
35 pharmacologically effective amount of a compound of formula (I) or a

pharmaceutically acceptable salt, biohydrolyzable ester, biohydrolyzable amide, biohydrolyzable carbamate, biohydrolyzable carbonate, biohydrolyzable ureide, solvate, hydrate, affinity reagent or prodrug thereof.

5 According to a further aspect of the present invention there is provided a method of treating a disease mediated by a kinase selected from the group consisting of cRaf1 kinase, p38 kinase, VEGFR kinase, Tie2 kinase and c-fms kinase, said method comprising the step of administering to a mammal in need thereof a pharmacologically effective amount of a compound of formula (I) or a
10 pharmaceutically acceptable salt, biohydrolyzable ester, biohydrolyzable amide, biohydrolyzable carbamate, biohydrolyzable carbonate, biohydrolyzable ureide, solvate, hydrate, affinity reagent or prodrug thereof.

15 According to a further aspect of the present invention there is provided a method of inhibiting tumor growth, preventing organ transplant rejection, healing a chronic wound, or of treating a disease state selected from the group consisting of restenosis, rheumatoid arthritis, angiogenesis, hepatic cirrhosis, atherosclerosis, glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, glomerulopathy,
20 psoriasis, asthma, diabetes mellitus, inflammation, and neurodegenerative disease, comprising the step of administering to a patient in need thereof a pharmacologically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, biohydrolyzable ester, biohydrolyzable amide, biohydrolyzable carbamate, biohydrolyzable carbonate,
25 biohydrolyzable ureide, solvate, hydrate, affinity reagent or prodrug thereof.

30 According to a further aspect of the present invention there is provided a method for the treatment of susceptible malignancies in an animal, e.g. a human, which comprises administering to the animal a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, biohydrolyzable ester, biohydrolyzable amide, biohydrolyzable carbamate, biohydrolyzable carbonate, biohydrolyzable ureide, solvate, hydrate, affinity reagent or prodrug thereof.

5 The invention further includes the use of a compound of formula (I) or one of its pharmaceutically acceptable salts, solvates, hydrates, affinity reagents or prodrugs, biohydrolyzable esters, amides, carbonates, amines, ureides or carbamates in the preparation of a medicament for the treatment of disorders mediated by protein kinase activity.

10 The invention further includes the use of a compound of formula (I) or one of its pharmaceutically acceptable salts, solvates, hydrates, affinity reagents or prodrugs, biohydrolyzable esters, amides, carbonates, amines, ureides or carbamates in the preparation of a medicament for the treatment of disorders mediated by disorders caused by a mutated ras gene.

15 The invention further includes the use of a compound of formula (I) or one of its pharmaceutically acceptable salts, solvates, hydrates, affinity reagents or prodrugs, biohydrolyzable esters, amides, carbonates, amines, ureides or carbamates in the preparation of a medicament for the treatment of disorders mediated by an upregulated tyrosine kinase signalling pathway.

20 The invention further includes the use of a compound of formula (I) or one of its pharmaceutically acceptable salts, solvates, hydrates, affinity reagents or prodrugs, biohydrolyzable esters, amides, carbonates, amines, ureides or carbamates in the preparation of a medicament for the treatment of disorders mediated by a mitogen activated protein kinase.

25 The invention further includes the use of a compound of formula (I) or one of its pharmaceutically acceptable salts, solvates, hydrates, affinity reagents or prodrugs, biohydrolyzable esters, amides, carbonates, amines, ureides or carbamates in the preparation of a medicament for the treatment of disorders mediated by cRaf kinase.

30 The invention further includes the use of a compound of formula (I) or one of its pharmaceutically acceptable salts, solvates, hydrates, affinity reagents or prodrugs, biohydrolyzable esters, amides, carbonates, amines, ureides or carbamates in the preparation of a medicament for inhibiting tumor growth,
35 preventing organ transplant rejection, healing a chronic wound, or of treating

5 a disease state selected from the group consisting of restenosis, rheumatoid arthritis, angiogenesis, hepatic cirrhosis, atherosclerosis, glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, glomerulopathy, psoriasis, asthma, diabetes mellitus, inflammation, and neurodegenerative disease.

10 Another aspect of the present invention provides the use of an active compound of formula (I) in the preparation of a medicament for the treatment of malignant tumors.

15 Another aspect of the present invention provides the use of an active compound of formula (I) in the preparation of a medicament for the treatment of blood vessel proliferative disorders such as angiogenic and vasculogenic disorders in cancer, ocular diseases, and restenosis.

20 Another aspect of the present invention provides the use of an active compound of formula (I) in the preparation of a medicament for the treatment of fibrotic disorders such as mesangial cell proliferative disorders.

25 Another aspect of the present invention provides the use of an active compound of formula (I) in the preparation of a medicament for the treatment of viral or eukaryotic infections.

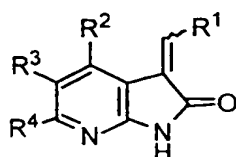
30 Another aspect of the present invention provides the use of an active compound of formula (I) in the preparation of a medicament for the treatment of inflammatory disorders.

35 Another aspect of the present invention provides the use of an active compound of formula (I) in coadministration with previously known anti-tumor therapies for more effective treatment of such tumors.

Compounds we have synthesized as part of the present invention which are currently preferred are listed in Tables 1, 1A, 2 and 2A, set forth below. Compounds are identified by the numbers shown in the first column; variables below in the rest of the columns are with reference to the generic structure (I).

Corresponding IUPAC nomenclature are disclosed in Tables 2 and 2A, respectively, below. Since all substituents at each point of substitution are capable of independent synthesis of each other, the tables are to be read as a matrix in which any combination of substituents is within the scope of the disclosure and claims of the invention.

Table 1



10

Number	R ¹	R ²	R ³	R ⁴
1		H		H
2		H		H
3		H		H
4		H		H
5		H	Br	H
6		H	Br	H
7		H		H

8		H		H
9		H		H
10		H		H
11		H		H
12		H		H
13		H		H
14		H		H
15		H		H
16		H		H
17		H	Br	H
18		H	Br	H
19		H	Br	H
20		H	Br	H

35

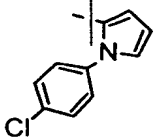
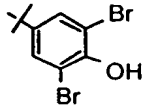
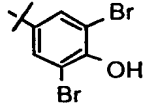
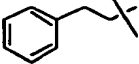
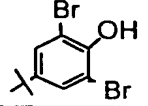
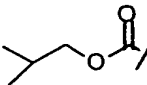
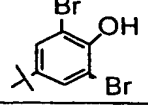
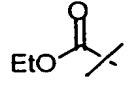
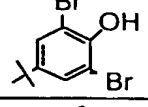
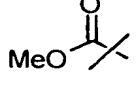
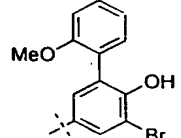
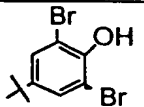
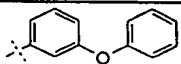
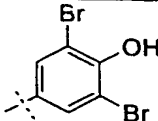
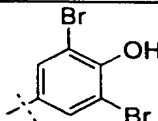
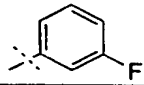
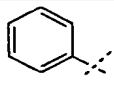
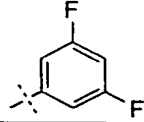
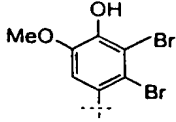
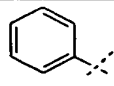
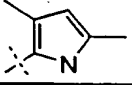
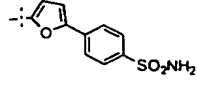



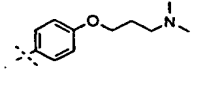



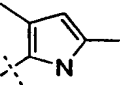

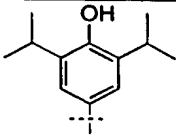
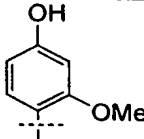
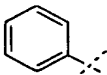
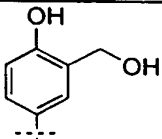
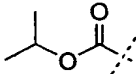
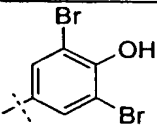
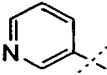
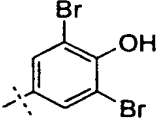

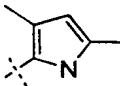

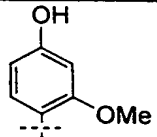

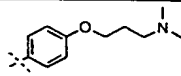
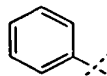
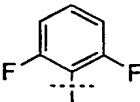

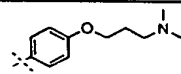
21		H	Br	H
22		H	-CH ₂ CH ₃	H
23		H		H
24		H		H
25		H		H
26		H		H
27		H	Br	H

Table 1A

Number	R ¹	R ²	R ³	R ⁴
28		H	Br	H
29		H	Br	H
30		H	H	Cl
31			Br	Cl
32		H		H
33		H	Br	H
34				H
35			Br	
36		H		H
37		H		
38		H		H

39		H		H
40		H		H
41		H	Br	H
42		H		H
43		H		H
44		H		H
45		H		H
46		H		H
47		H		H
48		H		H
49		H		H
50		H	H	Cl

38

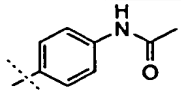
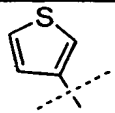
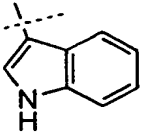
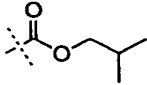
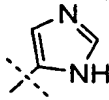

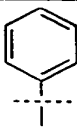
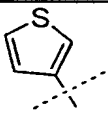
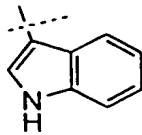
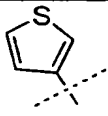
51		H		H
52		H		H
53		H		H
54		H		H
55		H		

Table 2

Compound	Name
1	3-(3,5-Dibromo-4-hydroxy-benzylidene)-5-thiophen-2-yl-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one
2	3-(3,5-Dibromo-4-hydroxy-benzylidene)-5-phenyl-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one
3	3-(3,5-Dibromo-4-hydroxy-benzylidene)-5-vinyl-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one
4	5-Acetyl-3-(3,5-dibromo-4-hydroxy-benzylidene)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one
5	5-Bromo-3-(4-hydroxy-3,5-dinitro-benzylidene)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one
6	5-Bromo-3-(3,5-dichloro-4-hydroxy-benzylidene)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one
7	3-(3,5-Dibromo-4-hydroxy-benzylidene)-5-furan-2-yl-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one
8	3-(3,5-Dibromo-4-hydroxy-benzylidene)-5-thiophen-3-yl-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one
9	4-[3-(3,5-Dibromo-4-hydroxy-benzylidene)-2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl]-benzenesulfonamide
10	3-(3,5-Dibromo-4-hydroxy-benzylidene)-5-phenylethynyl-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one
11	5-[3-(3,5-Dibromo-4-hydroxy-benzylidene)-2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl]-nicotinamide
12	3-(3,5-Dibromo-4-hydroxy-benzylidene)-2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid benzyl ester
13	Isopropyl-[(3,5-dibromo-4-hydroxyphenyl)methylidene]-2-oxo-1,2-dihydro-3H-pyrrolo[2,3-b]pyridine-5-carboxylate

14	5-(2-Bromoacetyl)-3-(3,5-dibromo-4-hydroxy-benzylidene)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one
15	3-(3,5-dibromo-4-hydroxy-benzylidene)-5-(2-methyl-thiazol-4-yl)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one
16	5-(2-Amino-thiazol-4-yl)-3-(3,5-dibromo-4-hydroxy-benzylidene)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one
17	5-Bromo-3-quinolin-3-ylmethylene-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one
18	5-Bromo-3-[4-(2-hydroxy-ethoxy)-benzylidene]-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one
19	5-(5-Bromo-2-oxo-1,2-dihydro-pyrrolo[2,3-b]pyridin-3-ylidenemethyl)benzoic acid
20	5-Bromo-3-[1-(3,5-dichlorophenyl)-1H-pyrrol-2-ylmethylene]-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one
21	5-Bromo-3-[1-(4-chlorophenyl)-1H-pyrrol-2-ylmethylene]-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one
22	3-(3,5-Dibromo-4-hydroxybenzylidene)-5-ethyl-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one
23	3-(3,5-Dibromo-4-hydroxy-benzylidene)-5-phenethyl-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one
24	3-(3,5-Dibromo-4-hydroxy-benzylidene)-2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid isobutyl ester
25	3-(3,5-Dibromo-4-hydroxy-benzylidene)-2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid ethyl ester
26	3-(3,5-Dibromo-4-hydroxy-benzylidene)-2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid methyl ester
27	3-(3-Bromo-4-hydroxy-5-(2'-methoxyphenyl)-benzylidene)-5-bromo-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one

Table 2A	
Compound	Name
28	5-Bromo-3-[(3,5-dibromo-4-hydroxyphenyl)methylidene]-1H-pyrrolo[2,3-b]pyridin-2-one
29	5-Bromo-3-[(3-phenoxyphenyl)methylidene]-1H-pyrrolo[2,3-b]pyridin-2-one
30	6-chloro-3-[(3,5-dibromo-4-hydroxyphenyl)methylidene]-1H-pyrrolo[2,3-b]pyridin-2-one
31	5-Bromo-6-chloro-3-[(3,5-dibromo-4-hydroxyphenyl)methylidene]-1H-pyrrolo[2,3-b]pyridin-2-one
32	3-[(3-Fluorophenyl)methylidene]-5-phenyl-1H-pyrrolo[2,3-b]pyridin-2-one
33	5-bromo-3-[3,5-difluorophenyl)methylidene]-1H-pyrrolo[2,3-b]pyridin-2-one
34	3-[(2,3-Dibromo-4-hydroxy-5-methoxyphenyl)methylidene]-5-phenyl-1H-pyrrolo[2,3-b]pyridin-2-one
35	5-bromo-3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylidene]-1H-pyrrolo[2,3-b]pyridin-2-one
36	4-(5-{[2-Oxo-5-(3-thienyl)-1,2-dihydro-3H-pyrrolo[2,3-b]pyridin-3-ylidene]methyl}-2-furyl)benzenesulfonamide
37	3-[2-Furylmethylidene]-5-(3-thienyl)-1H-pyrrolo[2,3-b]pyridin-2-one
38	3-(4-[3-(dimethylamino)propoxy]phenylmethylidene)-5-(3-thienyl)-1H-pyrrolo[2,3-b]pyridin-2-one
39	5-(3-thienyl)-3-[2-thienylmethylidene]-1H-pyrrolo[2,3-b]pyridin-2-one
40	3-[3,5-dimethyl-1H-pyrrol-2-yl)methylidene]-5-(3-thienyl)-1H-pyrrolo[2,3-b]pyridin-2-one
41	5-Bromo-3-[(4-hydroxy-3,5-diisopropylphenyl)methylidene]-1H-pyrrolo[2,3-b]pyridin-2-one

	one
42	3-[(4-Hydroxy-2-methoxyphenyl)methylidene]-5-phenyl-1H-pyrrolo[2,3-b]pyridin-2-one
43	Isopropyl 3-[[4-hydroxy-3-(hydroxymethyl)phenyl]methylidene]-2-oxo-1,2-dihydro-3H-pyrrolo[2,3-b]pyridine-5-carboxylate
44	3-[(3,5-Dibromo-4-hydroxyphenyl)methylidene]-5-(3-pyridinyl)-1H-pyrrolo[2,3-b]pyridin-2-one
45	3-[(3,5-Dichloro-4-hydroxyphenyl)methylidene]-5-(2-furyl)-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one
46	3-[(3,5-Dimethyl-1H-pyrrol-2-yl)methylidene]-5-(2-furyl)-1H-pyrrolo[2,3-b]pyridin-2-one
47	5-(2-Furyl)-3-[(4-hydroxy-2-methoxyphenyl)methylidene]-1H-pyrrolo[2,3-b]pyridin-2-one
48	3-[(4-[3-(Dimethylamino)propoxy]phenyl)methylidene]-5-phenyl-1H-pyrrolo[2,3-b]pyridin-2-one
49	3-[(2,6-Difluorophenyl)methylidene]-5-(3-thienyl)-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one
50	6-Chloro-3-[(4-[3-(dimethylamino)propoxy]phenyl)methylidene]-1H-pyrrolo[2,3-b]pyridin-2-one
51	N-(4-[(2-Oxo-5-(3-thienyl)-1,2-dihydro-3H-pyrrolo[2,3-b]pyridin-3-ylidene)methyl]phenyl)acetamide
52	Isobutyl 2-oxo-3-[(2-pyridinylmethylidene)-1,2-dihydro-3H-pyrrolo[2,3-b]pyridine-5-carboxylate
53	3-[1H-Imidazol-4-ylmethylidene]-5-phenyl-1H-pyrrolo[2,3-b]pyridin-2-one
54	3-[Phenylmethylidene]-5-(3-thienyl)-1H-pyrrolo[2,3-b]pyridin-2-one
55	3-[1H-Indol-3-ylmethylidene]-5-(3-thienyl)-1H-pyrrolo[2,3-b]pyridin-2-one

Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid or by reacting the acid with a suitable organic or inorganic base. Representative salts include the following salts: Acetate, Aluminum, Benzenesulfonate, Benzoate,

Bicarbonate, Bisulfate, Bitartrate, Borate, Bromide, Calcium, Calcium Edetate, Camsylate, Carbonate, Chloride, Chloroprocaine, Choline, Clavulanate, Citrate, Dibenzylethylenediamine, Diethanolamine, Dihydrochloride, Edetate, Edisylate, Estolate, Esylate, Ethylenediamine, Fumarate, Gluceptate, Gluconate, Glutamate, Glycollylarsanilate, Hexylresorcinate, Hydrabamine, Hydrobromide, Hydrochloride, Hydroxynaphthoate, Iodide, Isethionate, Lactate, Lithium, Lactobionate, Laurate, Malate, Maleate, Magnesium, Mandelate, Mesylate, Methylbromide, Methylnitrate, Methylsulfate, Monopotassium Maleate, Mucate, Napsylate, Nitrate, N-methylglucamine, Oxalate, Pamoate (Embonate), Palmitate, Pantothenate, Phosphate/diphosphate, Polygalacturonate, Potassium, Procaine, Salicylate, Sodium, Stearate, Subacetate, Succinate, Sulfate, Tannate, Tartrate, Teoclate, Tosylate, Triethanolamine, Triethiodide, Trimethylammonium and Valerate.

Salts which are not pharmaceutically acceptable may be useful in the preparation of intermediates towards the final synthesis of compounds of formula (I) and these form a further aspect of the invention.

Also included within the scope of the invention are the individual chiral isomers of the compounds represented by formula (I) above as well as any wholly or partially equilibrated mixtures thereof. The present invention also covers the individual isomers of the compounds represented by the formulas above as mixtures with isomers thereof in which one or more chiral centers are inverted.

For the following defined terms, these definitions shall be applied, unless a different definition is given in the claims or elsewhere in this specification.

As used herein, the term "aliphatic" refers to the terms alkyl, alkylene, alkenyl, alkenylene, alkynyl and alkynylene, as those terms are defined below.

As used herein, the term "lower" refers to a group having between one and six carbons, unless specified or implied otherwise in the text.

As used herein, the term "alkyl" refers to a straight or branched chain hydrocarbon having a specified number of carbon atoms, optionally substituted with substituents such as lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl or others as identified throughout this specification and claims, multiple degrees of substitution being allowed. Examples of "alkyl" as used herein include , but are not limited to, n-butyl, n-pentyl, isobutyl, and isopropyl, and the like. The term "alkyl" as used herein also generically refers to the below-defined terms, "alkylene", "alkenyl", "alkenylene", "alkynyl" and "alkynylene".

As used herein, the term "alkylene" refers to a straight or branched chain divalent hydrocarbon radical having from one to ten carbon atoms, optionally substituted with substituents such as lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl or others as identified throughout this specification and claims, multiple degrees of substitution being allowed. Examples of "alkylene" as used herein include, but are not limited to, methylene, ethylene, and the like.

As used herein, the term "alkenyl" refers to a hydrocarbon radical having from two to ten carbons and at least one carbon - carbon double bond, optionally substituted with substituents such as lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl or others as identified throughout this specification and claims, multiple degrees of substitution being allowed.

As used herein, the term "alkenylene" refers to an straight or branched chain divalent hydrocarbon radical having from two to ten carbon atoms and one or more carbon - carbon double bonds, optionally substituted with substituents such as lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed or others as identified throughout this specification and claims. Examples of "alkenylene" as used herein include, but are not limited to, ethene-1,2-diyl, propene-1,3-diyl, methylene-diyl, and the like.

As used herein, the term "alkynyl" refers to a hydrocarbon radical having from two to ten carbons and at least one carbon - carbon triple bond, optionally substituted with substituents such as lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by substituents such as alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl or others as identified throughout this specification and claims, multiple degrees of substitution being allowed.

As used herein, the term "alkynylene" refers to a straight or branched chain divalent hydrocarbon radical having from two to ten carbon atoms and one or more carbon - carbon triple bonds, optionally substituted with substituents such as lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl or others as identified throughout this specification and claims, multiple degrees of substitution being allowed. Examples of "alkynylene" as used herein include, but are not limited to, ethyne-1,2-diyl, propyne-1,3-diyl, and the like.

As used herein, "cycloalkyl" refers to an alicyclic hydrocarbon group with one or more degrees of unsaturation, having from three to twelve carbon atoms, optionally substituted with substituents such as lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl or others as identified throughout this specification and claims, multiple degrees of substitution being allowed. "Cycloalkyl" includes by way of example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl, and the like. The term "cycloalkyl" as used herein also generically refers to the below defined terms "cycloalkylene", "cycloalkenyl", and "cycloalkenylene".

As used herein, the term "cycloalkylene" refers to a non-aromatic alicyclic divalent hydrocarbon radical having from three to twelve carbon atoms, optionally substituted with substituents such as lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl or others as identified throughout this specification and claims, multiple degrees of substitution being allowed. Examples of "cycloalkylene" as used herein include, but are not limited to, cyclopropyl-1,1-diyl, cyclopropyl-1,2-diyl, cyclobutyl-1,2-diyl, cyclopentyl-1,3-diyl, cyclohexyl-1,4-diyl, cycloheptyl-1,4-diyl, or cyclooctyl-1,5-diyl, and the like.

As used herein, the term "cycloalkenyl" refers to a substituted alicyclic hydrocarbon radical having from three to twelve carbon atoms and at least one carbon-carbon double bond in the ring system, optionally substituted with substituents such as lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower

perfluoroalkyl or others as identified throughout this specification and claims, multiple degrees of substitution being allowed. Examples of "cycloalkenylene" as used herein include, but are not limited to, 1-cyclopentene-3-yl, 1-cyclohexene-3-yl, 1-cycloheptene-4-yl, and the like.

5

10

15

As used herein, the term "cycloalkenylene" refers to a substituted alicyclic divalent hydrocarbon radical having from three to twelve carbon atoms and at least one carbon-carbon double bond in the ring system, optionally substituted with substituents such as lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl or others as identified throughout this specification and claims, multiple degrees of substitution being allowed. Examples of "cycloalkenylene" as used herein include, but are not limited to, 4,5-cyclopentene-1,3-diyl, 3,4-cyclohexene-1,1-diyl, and the like.

20

25

30

As used herein, the term "heterocyclic" or the term "heterocyclyl" refers to a three to twelve-membered heterocyclic ring having one or more degrees of unsaturation containing one or more heteroatomic substitutions selected from S, SO, SO₂, O, or N, optionally substituted with substituents such as lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, lower perfluoroalkyl, or others as identified throughout this specification and claims, multiple degrees of substitution being allowed. Such a ring may be optionally fused to one or more of another "heterocyclic" ring(s) or cycloalkyl ring(s). Examples of "heterocyclic" include, but are not limited to, tetrahydrofuran, pyran, 1,4-dioxane, 1,3-dioxane, piperidine, pyrrolidine, morpholine, tetrahydrothiopyran, tetrahydrothiophene, and the like. A more comprehensive listing of such rings is found in the Summary of the Invention.

The term "heterocyclic" also generically refers to the below-defined terms "heterocyclylene", "heteroaryl", and "heteroarylene".

As used herein, the term "heterocyclylene" refers to a three to twelve-membered heterocyclic ring diradical having one or more degrees of unsaturation containing one or more heteroatoms selected from S, SO, SO₂, O, or N, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, lower perfluoroalkyl, or others as identified throughout this specification and claims or others as identified throughout this specification and claims, multiple degrees of substitution being allowed. Such a ring may be optionally fused to one or more benzene rings or to one or more of another "heterocyclic" rings or cycloalkyl rings. Examples of "heterocyclylene" include, but are not limited to, tetrahydrofuran-2,5-diyl, morpholine-2,3-diyl, pyran-2,4-diyl, 1,4-dioxane-2,3-diyl, 1,3-dioxane-2,4-diyl, piperidine-2,4-diyl, piperidine-1,4-diyl, pyrrolidine-1,3-diyl, morpholine-2,4-diyl, and the like. A more comprehensive listing of such rings is found in the Summary of the Invention.

As used herein, the term "aryl" refers to a benzene ring or to an optionally substituted benzene ring system fused to one or more optionally substituted benzene rings, which is referred to herein as a "biaryl", optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, lower perfluoroalkyl, heteroaryl, or aryl or others as identified throughout this specification and claims, multiple degrees of substitution being allowed. Examples of aryl include, but are not limited to, phenyl, 2-naphthyl, 1-naphthyl, biphenyl, and the like.

As used herein, the term "arylene" refers to a benzene ring diradical or to a benzene ring system diradical fused to one or more optionally substituted benzene rings, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, lower perfluoroalkyl, heteroaryl, or aryl or others as identified throughout this specification and claims, multiple degrees of substitution being allowed. Examples of "arylene" include, but are not limited to, benzene-1,4-diyl, naphthalene-1,8-diyl, anthracene-1,4-diyl, and the like.

As used herein, the term "heteroaryl" refers to a five - to seven - membered aromatic ring, or to a polycyclic heterocyclic aromatic ring, containing one or more nitrogen, oxygen, or sulfur heteroatoms, where N-oxides and sulfur monoxides and sulfur dioxides are permissible heteroaromatic substitutions, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, lower perfluoroalkyl, heteroaryl, or others identified throughout this specification and claims, multiple degrees of substitution being allowed. For polycyclic aromatic ring systems, one or more of the rings may contain one or more heteroatoms. Examples of "heteroaryl" used herein are furan, thiophene, pyrrole, imidazole, pyrazole, triazole, tetrazole, thiazole, oxazole, isoxazole, oxadiazole, thiadiazole, isothiazole, pyridine, pyridazine, pyrazine, pyrimidine, quinoline, isoquinoline, benzofuran, benzothiophene, indole, and indazole, and the like. A more comprehensive listing of such rings is found in the Summary of the Invention.

The term "heteroaryl" also generically refers to the below-defined term "heteroarylene".

As used herein, the term "heteroarylene" refers to a five - to seven - membered aromatic ring diradical, or to a polycyclic heterocyclic aromatic ring diradical, containing one or more nitrogen, oxygen, or sulfur heteroatoms, where N-oxides and sulfur monoxides and sulfur dioxides are permissible heteroaromatic substitutions, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, lower perfluoroalkyl, heteroaryl, or aryl, multiple degrees of substitution being allowed. For polycyclic aromatic ring system diradicals, one or more of the rings may contain one or more heteroatoms. Examples of "heteroarylene" used herein are furan-2,5-diyl, thiophene-2,4-diyl, 1,3,4-oxadiazole-2,5-diyl, 1,3,4-thiadiazole-2,5-diyl, 1,3-thiazole-2,4-diyl, 1,3-thiazole-2,5-diyl, pyridine-2,4-diyl, pyridine-2,3-diyl, pyridine-2,5-diyl, pyrimidine-2,4-diyl, quinoline-2,3-diyl, and the like.

As used herein, the term "alkoxy" refers to the group R_aO- , where R_a is alkyl, alkenyl or alkynyl.

As used herein, the term "alkylsulfanyl" refers to the group R_aS- , where R_a is alkyl, alkenyl, or alkynyl.

As used herein, the term "alkenylsulfanyl" refers to the group R_aS- , where R_a is alkenyl or alkynyl.

As used herein, the term "alkylsulfenyl" refers to the group $R_aS(O)-$, where R_a is alkyl, alkenyl or alkynyl.

As used herein, the term "alkylsulfonyl" refers to the group R_aSO_2- , where R_a is alkyl, alkenyl or alkynyl.

5 As used herein, the term "acyl" refers to the group $R_aC(O)-$, where R_a is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, or heterocyclyl.

As used herein, the term "aroyl" refers to the group $R_aC(O)-$, where R_a is aryl.

10 As used herein, the term "heteroaroyl" refers to the group $R_aC(O)-$, where R_a is heteroaryl.

As used herein, the term "alkoxycarbonyl" refers to the group $R_aOC(O)-$, where R_a is alkyl.

15 As used herein, the term "carbamate" or "carbamoyl" refers to the group $R_aR_bNC(O)-$, where R_a and R_b are hydrogen, alkyl, aryl, heterocyclyl or heteroaryl.

20 As used herein, the term "alkylcarbonyloxy" refers to the group $R_aC(O)O-$, where R_a is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, or heterocyclyl.

As used herein, the term "aroyloxy" refers to the group $R_aC(O)O-$, where R_a is aryl.

25 As used herein, the term "heteroaroyloxy" refers to the group $R_aC(O)O-$, where R_a is heteroaryl.

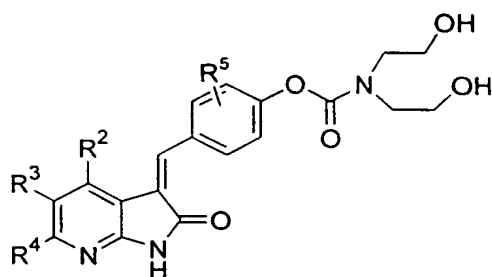
30 From time to time in this specification and claims, the term "optionally" appears, followed by recitation of one or more chemical substitutions or reactions. As used herein, the term "optionally" means that the subsequently described substitution or reaction(s) may or may not occur at the option of one of ordinary skill in the art conducting the substitution or reaction, and includes both those situations where the substitution or reaction has occurred and those where it has not occurred.

As used herein, the term "substituted" refers to substitution with the named substituent or substituents, multiple degrees of substitution being allowed.

5 As used herein, the terms "bears" or "bearing" can refer to in-line insertion substitutions at any position along the above-defined aliphatic, alkyl, alkenyl, alkynyl or cycloalkyl substituents' chain lengths, with one or more of any of -O-, -S-, -S(O)-, -S(O)₂-, -N(H)-, or -N(aliphatic)-, including, for example, -CH₂-O-CH₂-, -CH₂-SO₂-CH₂-, -CH₂-NH-CH₃ and so forth.

10 As used herein, the term "solvate" is a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula (I)) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Solvents may be, by way of example, water, ethanol, or
15 acetic acid.

As used herein, the terms "biohydrolyzable carbamate", "biohydrolyzable carbonate" and "biohydrolyzable ureide" is a carbamate, carbonate or ureide, respectively, of a drug substance (in this invention, a compound of general
20 formula (I) which either: a) does not interfere with the biological activity of the parent substance but confers on that substance advantageous properties in vivo such as uptake, duration of action, onset of action, and the like; or b) is biologically inactive but is readily converted in vivo by the subject to the biologically active principle. The advantage is that, for example, the
25 biohydrolyzable carbamate is orally absorbed from the gut and is transformed to (I) in plasma. Many examples of such are known in the art, and include by way of example carbamates of lower alkylamines, substituted ethylenediamines, aminoacids, hydroxyalkylamines, heterocyclic and heteroaromatic amines, polyether amines, and the like. An example of such a biohydrolyzable carbamate
30 applied to the general formula (I) is illustrated below in general formula (A)



(A)

Other examples of biohydrolyzable carbamates include those situations in which R^5 is an OH moiety and said OH is conjugated with a carbamoyl conjugate to yield a biohydrolyzable carbamate wherein said carbamoyl conjugate is selected from the group consisting of diethylaminocarbonyl, N-(2-hydroxyethyl)aminocarbonyl, N,N,-bis(2-hydroxyethyl)aminocarbonyl, 4-morpholinocarbonyl and 4-methyl-1-piperazinylcarbonyl.

As used herein, the term "biohydrolyzable ester" is an ester of a drug substance (in this invention, a compound of general formula (I) which either a) does not interfere with the biological activity of the parent substance but confers on that substance advantageous properties in vivo such as duration of action, onset of action, and the like, or b) is biologically inactive but is readily converted in vivo by the subject to the biologically active principle. The advantage is that, for example, the biohydrolyzable ester is orally absorbed from the gut and is transformed to (I) in plasma. Many examples of such are known in the art and include by way of example lower alkyl esters, lower acyloxy-alkyl esters, lower alkoxyacyloxyalkyl esters, alkoxyacyloxy esters, alkyl acylamino alkyl esters, and choline esters.

As used herein, the term "biohydrolyzable amide" is an amide of a drug substance (in this invention, a compound of general formula (I) which either a) does not interfere with the biological activity of the parent substance but confers on that substance advantageous properties in vivo such as duration of action, onset of action, and the like, or b) is biologically inactive but is readily converted in vivo by the subject to the biologically active principle. The advantage is that, for example, the biohydrolyzable amide is orally absorbed from the gut and is transformed to (I) in plasma. Many examples of such are known in the art and include by way of example lower alkyl amides, α -amino acid amides, alkoxyacyl amides, and alkylaminoalkylcarbonyl amides.

As used herein, the term "prodrug" includes biohydrolyzable amides and biohydrolyzable esters and biohydrolyzable carbamates, carbonates, and ureides, and also encompasses: a) compounds in which the biohydrolyzable functionality in such a prodrug is encompassed in the compound of formula (I), for example, the lactam formed by a carboxylic group in R^2 and an amine in R^3 ; and b) compounds which may be oxidized or reduced biologically at a given functional group to yield drug substances of formula (I). Examples of these functional groups are, but are not limited to, 1,4-dihydropyridine, N-alkylcarbonyl-1,4-dihydropyridine, 1,4-cyclohexadiene, tert-butyl, and the like.

As used herein, the term "hydrate" means a crystalline substance containing one or more molecules of water of crystallization.

As used herein, the term "affinity reagent" is a group attached to the compound of formula (I) which does not affect its in vitro biological activity, allowing the compound to bind to a target, yet such a group binds strongly to a third component allowing: a) characterization of the target as to localization within a cell or other organism component, perhaps by visualization by fluorescence or radiography; or b) facile separation of the target from an unknown mixture of targets, whether proteinaceous or not proteinaceous. An example of an affinity

reagent according to criterion (b) would be biotin either directly attached to (I) or linked with a spacer of one to 50 atoms selected from the group consisting of C, H, O, N, S, or P in any combination. An example of an affinity reagent according to criterion (a) above would be fluorescein, either directly attached to (I) or linked with a spacer of one to 50 atoms selected from the group consisting of C, H, O, N, S, or P in any combination.

The term "pharmacologically effective amount" shall mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by a researcher or clinician.

Whenever the terms "alkyl" or "aryl" or either of their prefix roots appear in a name of a substituent (e.g. arylalkoxyaryloxy) they shall be interpreted as including those limitations given above for "aliphatic" and "aryl". Alkyl or cycloalkyl substituents shall be recognized as being functionally equivalent to those having one or more degrees of unsaturation. Designated numbers of carbon atoms (e.g. C₁₋₁₀) shall refer independently to the number of carbon atoms in an aliphatic or cycloaliphatic moiety or to the aliphatic portion of a larger substituent.

As used herein, the term "oxo" shall refer to the substituent =O.

As used herein, the term "halogen" or "halo" shall include iodine, bromine, chlorine and fluorine.

As used herein, the term "mercapto" shall refer to the substituent -SH.

As used herein, the term "carboxy" shall refer to the substituent -COOH.

As used herein, the term "cyano" shall refer to the substituent -CN.

As used herein, the term "aminosulfonyl" shall refer to the substituent -SO₂NH₂.

As used herein, the term "carbamoyl" shall refer to the substituent $-C(O)NH_2$.

As used herein, the term "sulfanyl" shall refer to the substituent $-S-$.

5

As used herein, the term "sulfenyl" shall refer to the substituent $-S(O)-$.

As used herein, the term "sulfonyl" shall refer to the substituent $-S(O)_2-$.

10 The compounds of formula (I) can be prepared readily according to the following
reaction Schemes (in which all variables are as defined before) and Examples or
modifications thereof using readily available starting materials, reagents and
conventional synthesis procedures. In these reactions, it is also possible to make
15 use of variants which are themselves known to those of ordinary skill in this art,
but are not mentioned in greater detail.

Preparation

20 The most preferred compounds of the invention are any or all of those specifically
set forth in these examples. These compounds are not, however, to be construed
as forming the only genus that is considered as the invention, and any
combination of the compounds or their moieties may itself describe a genus of the
invention. The following examples further illustrate details for the preparation of
the compounds of the present invention. Those skilled in the art will readily
25 understand that known variations of the conditions and processes of the following
preparative procedures can be used to prepare these compounds. All
temperatures are degrees Celsius unless noted otherwise.

Abbreviations used in the Examples are as follows:

30 g = grams
mg, = milligrams
L = liters

	mL	= milliliters
	μL	= microliters
	M	= molar
	N	= normal
5	mM	= millimolar
	i.v.	= intravenous
	p.o.	= per oral
	s.c.	= subcutaneous
	Hz	= hertz
10	mol	= moles
	mmol	= millimoles
	mbar	= millibar
	psi	= pounds per square inch
	rt	= room temperature
15	min	= minutes
	hr	= hours
	mp	= melting point
	TLC	= thin layer chromatography
	R _f	= relative TLC mobility
20	MS	= mass spectrometry
	NMR	= nuclear magnetic resonance spectroscopy
	APCI	= atmospheric pressure chemical ionization
	ESI	= electrospray ionization
	m/z	= mass to charge ratio
25	HPLC	= high pressure liquid chromatography
	t _r	= retention time
	Pd/C	= palladium on activated carbon
	ether	= diethyl ether
	MeOH	= methanol
30	EtOAc	= ethyl acetate
	TEA	= triethylamine
	DIEA	= diisopropylethylamine

THF = tetrahydrofuran
DMF = N, N-dimethylformamide
DMSO = dimethylsulfoxide
DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone
5 LAH = lithium aluminum hydride
TFA = trifluoroacetic acid
HCl = hydrochloric acid
LDA = lithium diisopropylamide
THP = tetrahydropyranyl
10 NMM = N-methylmorpholine, 4-methylmorpholine
HMPA = hexamethylphosphoric triamide
DMPU = 1,3-dimethylpropylene urea
d = days
ppm = parts per million
15 kD = kiloDalton
LPS = lipopolysaccharide
PMA = phorbol myristate acetate
SPA = scintillation proximity assay
EDTA = ethylenediamine tetraacetic acid
20 FBS = fetal bovine serum
PBS = phosphate buffered saline solution

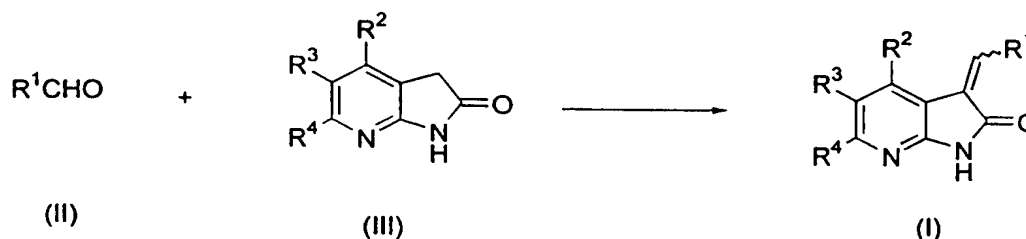
Several of the following examples represent single E isomers, single Z isomers and mixtures of E/Z isomers. Determination of the E and Z isomers can be done
25 by analytical methods such as x-ray crystallography, ^1H NMR and ^{13}C NMR.

GENERAL REACTION SCHEMES

Compounds of the invention may be prepared by methods known in the art, where such a method is shown in the Reaction Schemes shown below.
30

Reaction Scheme 1

59



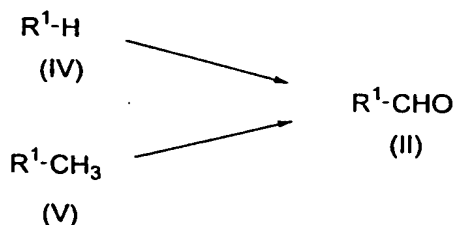
R^1 , R^2 , R^3 , R^4 are defined as above for formula (I).

The conversion of (II) and (III) to (I) involves methods known as the aldol condensation followed by elimination which is well described in "Advanced Organic Chemistry," Carey and Sundberg, 3rd edition, Plenum Press, 1990, principally contained in chapter 2 of part B. The reaction may be conducted using acid (for example concentrated HCl) in combination with a suitable solvent, such as acetic acid at temperatures ranging from 25 °C to 150 °C. Lewis acid or catalytic acid conditions may also be used such as a catalytic amount of para-toluenesulfonic acid or boron trifluoride etherate in a suitable solvent such as toluene at temperatures ranging from 25 °C to 125°C. Alternatively, basic conditions may be applied to effect an aldol/elimination reaction such as treatment with sodium hydride in a suitable solvent such as THF at temperatures ranging from -20 °C to 22 °C or treatment with pyrrolidine in ethyl alcohol at temperatures ranging from 25 °C to 80 °C. Some of these compounds of formula (I) may also be synthesized according to Reaction Scheme 1 by combining (II) and (III) in a suitable solvent such as toluene and heating at temperatures ranging from 40 °C to 125 °C for 1h to 7 days.

Aromatic, heterocyclic and heteroaromatic aldehydes of formula (II) are commercially available, or may be prepared by published procedures. Reaction Scheme 2 depicts two routes to readily synthesize substituted aromatic and heteroaromatic aldehydes that are not commercially available.

Reaction Scheme 2

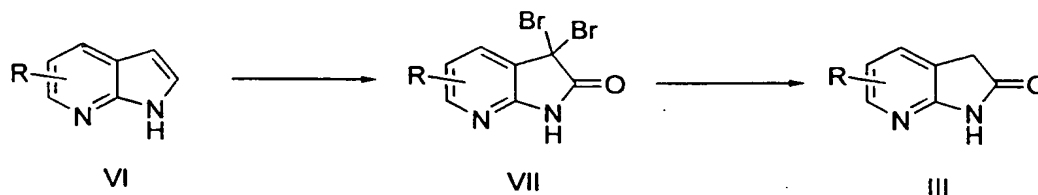
60



Generation of the substituted compounds of formula (II) may be obtained by a variety of methods by those skilled in the art. For example, the conversion of (IV) to (II) may be conducted by treating (IV) in a suitable solvent such as acetic acid with hexamethylenetetramine at a temperature of 90 °C to 130 °C. Preparation of the proper aldehydes may also be achieved via a well known Vilsmeier-Haak reaction (A. Vilsmeier, A. Haak, *Berichte*, 60, 119, 1927) wherein the formylation of aromatic or heteroaromatic compounds may be achieved by treatment with disubstituted formamide, such as *N,N*-dimethylformamide, and phosphorus oxychloride. Alternatively, (V) can be converted to (II) by treating (V) in a suitable solvent such as dioxane with reagents capable of oxidation, for example with a small amount of water with DDQ at a temperature of 0 °C to 140 °C. In addition to the above, one compound of formula (II) can be converted to another compound of formula (II) by a chemical transformation of the appropriate substituent or substituents. For example, when R¹ is substituted with an hydroxyl in (II), the conversion to a carbamate, carbonate, and ether is conducted by treating (II) in a suitable solvent such as THF with an alkylating agent such as chloromethyl-R, or an acylating agent such as alkylchloroformates and alkylcarbamoylchlorides in a suitable solvent such as dichloromethane.

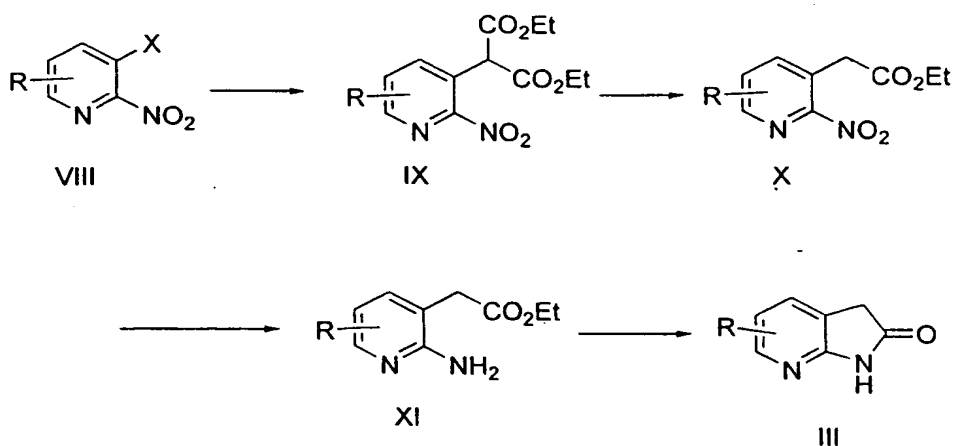
7-aza-oxindoles of formula (III) may be prepared by published procedures or variations of published procedures. Reaction Scheme 3 depicts a route to synthesize compounds of formula (III)

61

Reaction Scheme 3

5 A pyrrolopyridine of formula (VI) may be converted to (VII) utilizing a method well described in the literature (A. Marfat and M. Carta, *Tetrahedron letters*, 28(35) pp 4027-4030, 1987) by treatment with pyridinium perbromide in a suitable solvent such as t-butyl alcohol at a temperature of 25 °C. A compound of formula (VII)

10 may be converted to (III) by treatment with 10 % Pd/C in a suitable solvent such as anhydrous ethanol at 30 to 50 psi of hydrogen or by treatment with a saturated solution of ammonium chloride followed by treatment with activated zinc in a suitable solvent such as THF.

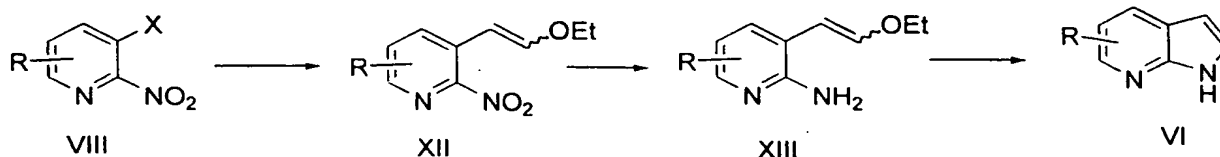
Reaction Scheme 4

15 An alternative route to synthesize appropriately substituted 7-aza-oxindoles of formula III is depicted in Reaction Scheme 4 beginning with substituted pyridines.

20 For example, where X is chlorine in compound VIII, the conversion of VIII to IX

may be conducted by treatment with the anion of diethyl malonate such as that prepared by treatment of diethyl malonate in a suitable solvent such as dimethylsulfoxide with sodium hydride. The decarboxylation of IX to obtain X may be conducted by heating IX in wet dimethyl sulfoxide containing a simple salt, such as lithium chloride which is well known in the literature (Krapcho, Synthesis, 805-822, 1982 or for another method Aneja, Hollis, Davies, Eaton, Tetrahedron Letters, 24, 4641, 1983). The conversion of X to XI may be conducted using a metal catalyst capable of reducing nitro groups to amino groups such as palladium on carbon in a suitable solvent such as ethanol under an atmosphere of hydrogen gas.

Reaction Scheme 5

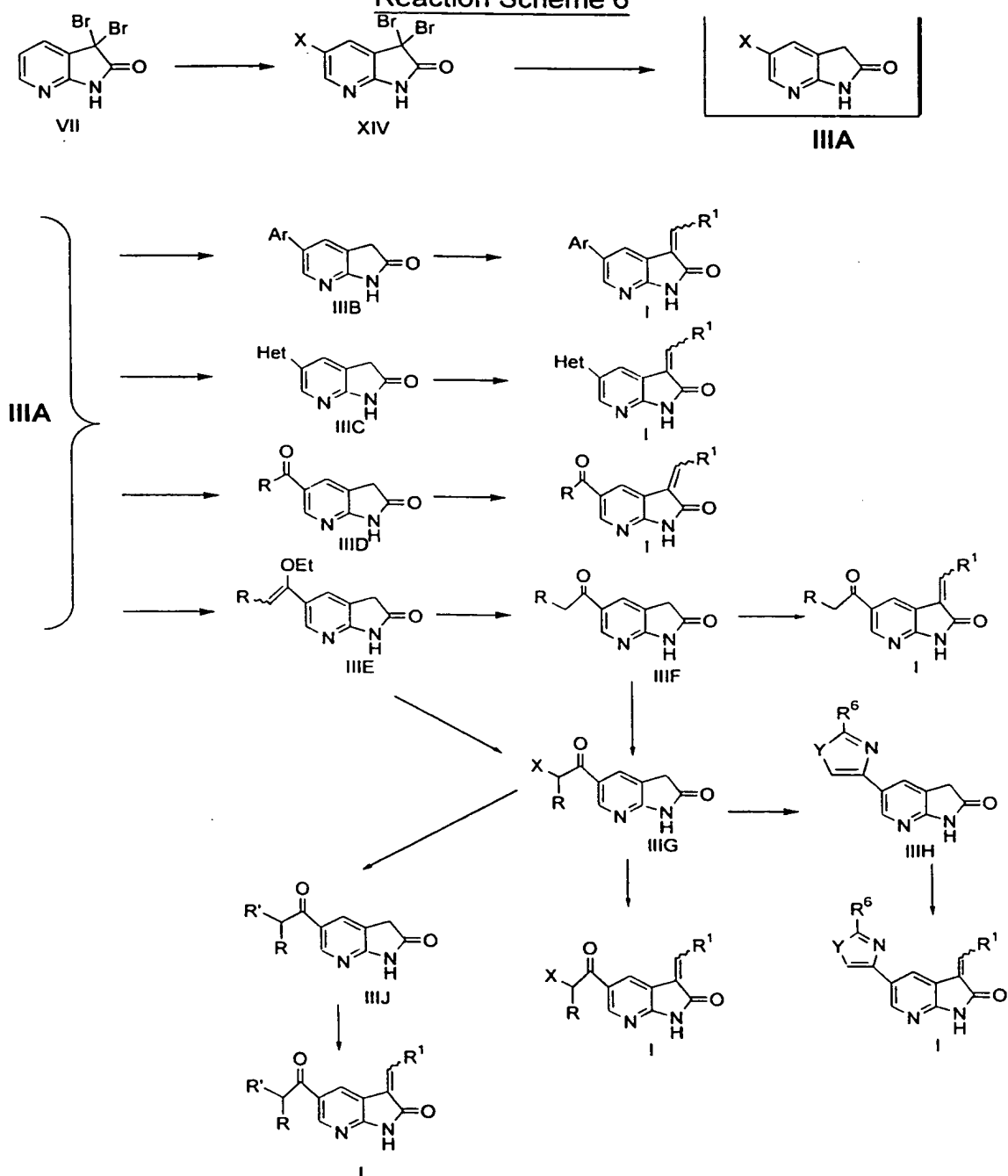


The syntheses of variously substituted pyrrolopyridines (VI) are well described in the literature (for example: T. Sakamoto, C. Satoh, Y. Kondo, H. Yamanaka Heterocycles 1992, 34(12), 2379-2384 and references cited therein). Reaction Scheme 5 depicts one convenient method that begins with commercially available pyridines VIII. The 2-ethoxyethenyl group may be introduced by a palladium-catalyzed reaction, for example, in the conversion of VIII to XII, by treatment of the pyridine derivative VIII with 1-ethoxy-2-tributylstannylethene and a palladium catalyst such as dichlorobis(triphenylphosphine)palladium(II) in a suitable solvent such as acetonitrile. A catalytic hydrogenation of XII may be conducted to obtain XIII under typical conditions such as treatment of XII with a metal catalyst capable of reducing a nitro group to an amino group such as W-2 Raney Nickel in a suitable solvent such as methanol under an atmosphere of hydrogen. The cyclization of XIII to a substituted pyrrolopyridine (VI) may be conducted utilizing

acidic conditions such as treatment of XIII with concentrated hydrochloric acid in a suitable solvent such as methanol at temperatures ranging from 0 °C to 100 °C.

5 In addition to incorporating substitutions into the initial stages of the synthesis, one compound of formula (III) can be converted to another compound of formula (III) by a chemical transformation to the appropriate substituent or substituents. For example, Reaction Scheme 6 depicts several well established transformations for the functionalization of a halogenated 7-aza-oxindole of formula (III) which, while demonstrated for a 5-position halogen, is not limited to
10 that position.

Reaction Scheme 6



By utilizing intermediate VII (from Reaction Scheme 3), an appropriately halogenated 7-azaoxindole may be obtained via intermediate XIV. Treatment of compounds of formula VII with bromine in the presence of aqueous sodium bicarbonate in a suitable solvent such as tertiary butyl alcohol to provide XIV may subsequently treated with a saturated aqueous solution of ammonium chloride and activated zinc dust to afford IIIA. Palladium catalyzed coupling of an iodo, bromo, or triflate functionalized reagent with the appropriately substituted organotin or boronate reagent will provide a broad range of the compounds of formula III. A compound of formula (IIIA) where X is bromo or iodo may be treated with a tributyltin heterocycle, for example 3-pyridyltributyltin, or a trialkyltin aryl compound such as 4-(tributyltin)benzene sulfonamide in the presence of a palladium catalyst, for example bistrisphenylphosphine dichloropalladium, in a suitable solvent, such as acetonitrile, to form (IIIB or IIIC). Alternately, (IIIA) may be converted to (IIIB or IIIC) by treatment with a heterocyclic or aromatic boronic acid, for example thiophene-3-boronic acid, in the presence of base, for example tetrakis-triphenyl phosphine palladium, in a suitable solvent, such as toluene, at a temperature of 22°C to 125°C. Similarly, where X is a hydroxyl group, it may first be converted to a triflate through standard conditions such as treatment with trifluoromethanesulfonic anhydride in the presence of a base such as sodium hydride in a suitable solvent such as benzene before the aforementioned chemistry is applied. It may be appreciated by one skilled in the art that such coupling reactions may be conducted through the alternative coupling partners in order to obtain compounds such as IIIB and IIIC. For example, the organotin or boron component may reside on the pyrrolopyridinone partner and the halogen or triflate on the aryl or heteroaromatic partner.

The conversion of IIIA to IIID where R is a lower alkoxy group may be conducted through a palladium mediated carbonylation reaction. This reaction may be carried out in a Parr shaker apparatus by treatment of IIIA with a lower alkyl alcohol such as ethanol in a suitable solvent such as dimethylsulfoxide in the presence of a palladium catalyst such as palladium diacetate and a suitable base such as triethylamine under an atmosphere of carbon monoxide gas. When R is

OH in IIID which can be synthesized in an analogous method as that described for the ester, the conversion of carboxylic acid IIID to esters and amides of formula IIID involves methods known in peptide chemistry, for example the reaction may be conducted using HOBt in combination with a dehydrating agent such as dicyclohexylcarbodiimide in a suitable solvent such as DMF. The conversion of IIIA to IIIF may be obtained through intermediate IIIE via a palladium catalyzed tin coupling reaction.

The conversion of IIIA to IIIE may be achieved by treatment of IIIA with a trialkyl(alkoxyvinyl)tin reagent such as tributyl(1-ethoxyvinyl)tin in the presence of a palladium catalyst such as dichlorobis(triphenylphosphine)palladium(II) in a suitable solvent such as acetonitrile. To obtain IIIF, IIIE may be treated with acid such as hydrochloric acid in a suitable solvent such as diethylether. Either IIIE or IIIF may be converted to a halomethyl ketone of formula IIIG by treatment with a halogenating reagent such as *N*-halosuccinimide in the presence of water in a suitable solvent such as tetrahydrofuran. Further functionalization to various heterocyclic groups may be achieved through treatment of IIIG with diversely substituted amidines, thioamides, ureas and substituted aminopyridines. For example, IIIG may be converted to IIIH by treating IIIG with thioacetamide in a suitable solvent such as acetic acid at a temperature of 22 °C to 100 °C. Compounds of formula IIIJ, where R' is, for example an alkyl or cyclic amine, may be obtained by treating IIIG with diverse nucleophiles such as amines in a suitable solvent such as THF at a temperature of 22 °C to 80 °C. These functionalized 7-aza-oxindoles (for example, IIIA, IIIB, IIIC, IIID, IIIF, IIIG, IIIH and IIIJ) may be converted to a compound of formula I using previously described chemistry.

PHARMACEUTICAL FORMULATION AND DOSES

The compounds of the present invention can be administered in such oral (including buccal and sublingual) dosage forms as tablets, capsules (each including timed release and sustained release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups and emulsions. Likewise, they may also be administered in nasal, ophthalmic, otic, rectal, topical, intravenous

(both bolus and infusion), intraperitoneal, intraarticular, subcutaneous or intramuscular inhalation or insufflation form, all using forms well known to those of ordinary skill in the pharmaceutical arts.

5 The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or
10 veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

A therapeutically effective amount of a compound or salt of the present invention will depend upon a number of factors including, for example, the age and weight
15 of the animal or patient, the precise condition requiring treatment and its severity, the nature of the formulation, and the route of administration, and will ultimately be at the discretion of the attendant physician or veterinarian.

Oral dosages of the present invention, when used for the indicated effects, will
20 range between about 0.1 to 300 mg/kg of body weight per day, and particularly 1 to 100 mg/kg of body weight per day. Oral dosage units will generally be administered in the range of from 1 to about 250 mg and more preferably from about 25 to 250 mg. The daily dosage for a 70 kg mammal will generally be in the range of about 10 mg to 5 grams of a compound of formula I. An effective
25 amount of a salt of the present invention may be determined as a proportion of the effective amount of the compound per se.

Topical application similarly may be once or more than once per day depending upon the usual medical considerations. Advantageously, compounds of the
30 present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, preferred compounds for the present invention can be administered

in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing and coloring agent can also be present.

Capsules are made by preparing a powder mixture as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or

sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant and pressing into tablets. A powder mixture is prepared by mixing the compound, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginat, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or an absorption agent such as bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acadia mucilage or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention can also be combined with free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages. -

Oral fluids such as solution, syrups and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl

alcohols and polyoxy ethylene sorbitol ethers, preservatives, flavor additive such as peppermint oil or saccharin, and the like can also be added.

5 Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, wax or the like.

10 The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

15 Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted
20 with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of
25 hydrogels.

The present invention includes pharmaceutical compositions containing 0.1 to 99.5%, more particularly, 0.5 to 90% of a compound of the formula (I) in combination with a pharmaceutically acceptable carrier.

30 Parenteral administration can be effected by utilizing liquid dosage unit forms such as sterile solutions and suspensions intended for subcutaneous,

intramuscular or intravenous injection. These are prepared by suspending or dissolving a measured amount of the compound in a non-toxic liquid vehicle suitable for injection such as aqueous oleaginous medium and sterilizing the suspension or solution.

5

Alternatively, a measured amount of the compound is placed in a vial and the vial and its contents are sterilized and sealed. An accompanying vial or vehicle can be provided for mixing prior to administration. Non-toxic salts and salt solutions can be added to render the injection isotonic. Stabilizers, preservations and emulsifiers can also be added.

10

Rectal administration can be effected utilizing suppositories in which the compound is admixed with low-melting water-soluble or insoluble solids such as polyethylene glycol, cocoa butter, higher ester as for example flavored aqueous solution, while elixirs are prepared through myristyl palmitate or mixtures thereof.

15

Topical formulations of the present invention may be presented as, for instance, ointments, creams or lotions, eye ointments and eye or ear drops, impregnated dressings and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams. The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as from about 1% up to about 98% of the formulation. More usually they will form up to about 80% of the formulation.

20

25

For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, tetrafluoroethane, heptafluoropropane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g.

30

gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

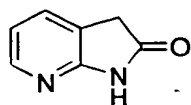
- 5 The preferred pharmaceutical compositions are those in a form suitable for oral administration, such as tablets and liquids and the like and topical formulations.

SYNTHESIS EXAMPLES

10 We now set forth a selected number of synthesis examples which illustrate the techniques used to obtain the compounds of the invention. It is believed that one of ordinary skill in the art will, in view of the synthesis schemes set forth above, be able to follow these procedures or modify them accordingly without undue experimentation in order to obtain any of the substitutions disclosed above. The following examples are illustrative embodiments of the invention, not limiting the scope of the invention in any way. Reagents are commercially available or are prepared according to procedures in the literature. Example numbers refer to those compounds listed in the tables above. ¹H NMR spectra were obtained on VARIAN Unity Plus NMR spectrophotometers at 300 or 400 Mhz. Mass spectra were obtained on Micromass Platform II mass spectrometers from Micromass Ltd. Altrincham, UK, using either Atmospheric Chemical Ionization (APCI) or Electrospray Ionization (ESI). Analytical thin layer chromatography (TLC) was used to verify the purity of some intermediates which could not be isolated or which were too unstable for full characterization, and to follow the progress of reactions. Unless otherwise stated, this was done using silica gel (Merck Silica Gel 60 F254). Unless otherwise stated, column chromatography for the purification of some compounds, used Merck Silica gel 60 (230-400 mesh), and the stated solvent system under pressure.

25 Methods for the synthesis of compounds of formula (III):

30 Example of Method A:



7-Azaoxindole

5 a) 3,3-Dibromo-7-azaoxindole

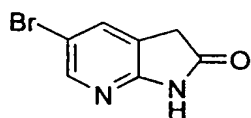
A solution of 7-azaindole (4.0g, 34 mmol) in tert-BuOH (200 mL) is stirred at room temperature and pyridinium perbromide (32.5g, 0.1 mol) is added in portions over 30 min. and the reaction mixture is stirred for 3 h. Pyridinium perbromide (10.8 g, 33 mmol) is added and the mixture is stirred for a further 2 h. The tert-BuOH is evaporated under reduced pressure and the residue is partitioned between water (300 mL) and EtOAc (300 mL). The organic layer is separated and the aqueous layer is extracted with EtOAc. The combined organic layers are washed with water (2 x 50 mL), and brine. The organic layer is dried over anhydrous MgSO₄, filtered and the solvent evaporated. Trituration of the residue with CH₂Cl₂ gives a white solid which is collected by filtration and dried under vacuum to give 3,3-dibromo-7-azaoxindole, 8.35g. ¹H NMR (d⁶ DMSO) δ 11.99 (s, 1H), 8.21 (dd, 1H, J = 5.1, 1.5 Hz), 8.00 (dd, 1H, J = 7.5, 1.5 Hz), 7.17 (dd, 1H, J = 7.5, 5.1 Hz). MS (+ve ES) 293 (28), (M+H), 147 (100).

20 b) 7-Azaoxindole

A solution of 3,3-dibromo-7-azaoxindole (2.0g, 7.2 mmol) in THF (50 mL) is stirred at room temperature and a saturated aqueous solution of NH₄Cl is added. Activated zinc powder is added and the reaction mixture is stirred for 2 h. The zinc is removed by filtration through a pad of diatomaceous earth and the organic layer is separated. The aqueous layer is extracted with THF (10 mL) and the combined organic layers are dried over anhydrous MgSO₄, filtered and evaporated. The residue is slurried in 10:1 CHCl₃:MeOH (15 mL) and filtered through a pad of silica gel and the filtrate is evaporated. The residue is triturated with water and the solid is collected by filtration and dried under vacuum to give 7-azaoxindole, 0.668g (70%). ¹H NMR (d⁶ DMSO) δ 10.94 (s, 1H), 8.02 (d, 1H, J =

5.2 Hz), 7.52 (d, 1H, J = 6.8 Hz), 6.90 (dd, 1H, J = 6.8, 5.2 Hz), 3.53 (s, 2H).
MS(AP-ve) 133 (100) (M-H)

Example of Method B:



5 Bromo-7-azaaxindole

a) 3,3,5 Tribromooxindole

A solution of 3,3-dibromo-7-azaaxindole (5.0 g, 13.4 mmol) in tert-BuOH (100 mL) and water (100 mL) is stirred at room temperature and bromine (5.5 g, 34.3 mmol) is added dropwise over 20 min. A saturated aqueous solution of sodium bicarbonate (approx. 15 mL) is added dropwise over 30 min to raise the pH of the solution to 6.5. The yellow solid formed is collected by filtration. The filtrate is condensed to approx. 100 mL and extracted with CHCl₃ (2 x 50 mL). The combined organic extracts are dried over anhydrous magnesium sulfate and the solvent is evaporated under reduced pressure to leave a yellow solid. The solids are combined and dried under vacuum to give 3,3,5 tribromooxindole as a yellow solid, 6.25 g (98%). ¹H NMR (CDCl₃) δ 9.4 (br s, 1H), 8.28 (d, 1H, J = 2 Hz), 7.95 (d, 1H, J = 2 Hz).

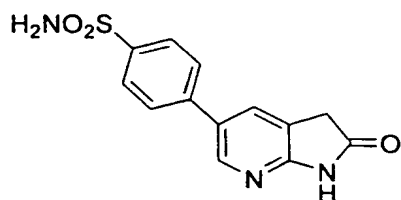
b) 5 Bromo-7-azaaxindole

A solution of 3,3,5 tribromooxindole (5.0 g, 13.4 mmol) in fresh THF (100 mL) is stirred at room temperature and a saturated aqueous solution of ammonium chloride (100 mL) is added. The flask is placed in a water bath and activated zinc dust (15.0 g, 230 mmol) is added. The mixture is stirred for 20 min and the zinc is removed by filtration through a pad of diatomaceous earth. The organic layer is separated and the aqueous layer is extracted with THF (20 mL). The combined organic layers were washed with saturated brine solution, dried over anhydrous magnesium sulfate and the solvent removed under reduced

pressure. The brown residue is triturated with water (20 mL) and the tan solid is collected by filtration and dried under vacuum to give 5-bromo-7-azaoxindole as a tan solid, 2.02 g (71%). ^1H NMR (d^6 DMSO) δ 11.13 (s, 1H), 8.15 (s, 1H), 8.76 (s, 1H), 3.57 (s, 2H). MS (AP -ve) 211 (100) (M-H).

5

Example of Method C:



5-(4-benzenesulfonamide)-7-azaoxindole

10

a) 4-(tributyltin) benzenesulfonamide

A mixture of 1 g (4.2 mmol) of 4-bromo benzene sulfonamide, 3.65 g (6.3 mmol) of bis(tributyltin), and 0.046 g (0.04 mmol) of palladium tetrakis triphenylphosphine in 25 ml of acetonitrile and 3 ml of toluene was heated to reflux for 18 hrs. After cooling to ambient temperature the reaction mixture was diluted with EtOAc and the excess bis(tributyltin) was removed via separatory funnel. The solvent was removed *in vacuo*, and the residue was chromatographed on silica gel (Hex/EtOAc 2:1) to afford 4-tributyltin benzene sulfonamide as white solid (0.97 g, 52%): ^1H NMR (DMSO-d_6): δ 0.81 (t, $J = 7.32$ Hz, 9H), 1.02-1.08 (m, 6H), 1.20-1.30 (m, 6H), 1.42-1.52 (m, 6H), 7.27 (s, 2H), 7.60 (d, $J = 7.87$ Hz, 2H), 7.72 (d, $J = 7.87$ Hz, 2H).

15

20

b) 5-(4-benzenesulfonamide)-7-azaoxindole

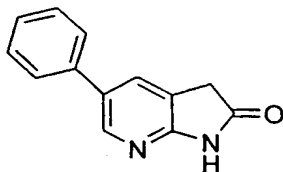
A mixture of 0.446 g (1 mmol) of 4-tributyltin benzene sulfonamide, 0.426 g (2 mmol) of 5-bromo-7-aza-oxindole, 0.497 g (3 mmol) of tetraethyl ammonium chloride, and 0.070 g (0.1 mmol) of bis(triphenylphosphine) palladium (II) chloride in 20 ml of acetonitrile was heated to reflux for 48 hrs. After cooling to ambient temperature the solvent was removed *in vacuo*, and the residue was chromatographed on silica gel (EtOAc) to afford 4-(2-Oxo-2,3-dihydro-1H-

25

pyrrolo[2,3-b]pyridin-5-yl) benzenesulfonamide as white solid (0.85 g, 29%): ^1H NMR ($\text{DMSO}-d_6$): δ 3.60 (s, 2H), 7.36 (s, 2H), 7.81 (d, $J = 8.8$ Hz, 2H), 7.85 (d, $J = 8.8$ Hz, 2H), 7.91 (d, $J = 2$ Hz, 1H), 8.41 (d, $J = 2$ Hz, 1H), 11.12 (s, 1H); ESI-MS: m/z 290 ($m+H$) $^+$.

5

Example of Method D:



5-phenyl-7-azaaxindole

10

a) 5-phenyl-7-azaaxindole

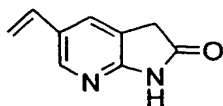
To a stirred mixture of 5-bromo-7-azaaxindole (213 mg, 1 mmol) and phenylboronic acid (183 mg, 1.5 mmol) in toluene (6 ml) and ethanol (6 ml) were added 1 M sodium carbonate solution (2.5 ml, 2.5 mmol), lithium chloride (127 mg, 3 mmol) and dichlorobis(triphenylphosphine)palladium(II) (35 mg, 0.05 mmol) under N_2 atmosphere. The reaction mixture was heated to reflux at 95 $^\circ\text{C}$ for 18 hours. The reaction mixture was diluted with chloroform (50 ml) and washed with brine (20 ml). The aqueous layer was thoroughly extracted with chloroform. The combined organic layers were dried over anhydrous MgSO_4 , filtered and evaporated under vacuum to give crude product. Trituation of the crude product with diethyl ether yielded 5-phenyl-7-azaaxindole as a yellow solid (108 mg, 51.4%). ^1H NMR (d^6 DMSO): δ 11.04 (s, 1H), 8.32 (s, 1H), 7.83 (s, 1H), 7.60 (d, 2H, $J = 7.4$ Hz), 7.44 (t, 2H, $J = 7.4$ Hz), 7.32 (t, 1H, $J = 7.4$ Hz), 3.58 (s, 2H). MS (-ve APCI): 210 (48, M^+), 209 (100, $M-H$).

15

20

25

Example of Method E:

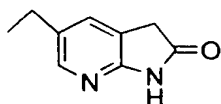


5-vinyl-7-azaaxindole

a) 5-vinyl-7-azaoxindole

To a stirred mixture of 5-bromo-7-azaoxindole (426 mg, 2 mmol) in acetonitrile (7 ml) were added tributyl(vinyl)tin (0.7 ml, 2.4 mmol), tetraethylammonium chloride (331 mg, 2 mmol), and dichlorobis(triphenylphosphine)palladium(II) (70.3 mg, 0.1 mmol) under N₂ atmosphere. The reaction mixture was heated to reflux at 95 °C for 22 hours. The reaction mixture was diluted with diethyl ether (100 ml) and washed with 2 M potassium fluoride solution (20 ml). The aqueous layer was thoroughly extracted with diethyl ether. The combined organic layers were dried over anhydrous MgSO₄, filtered and evaporated under vacuum to give crude product. Trituation of the crude product with diethyl ether yielded 5-vinyl-7-azaoxindole as a yellow solid (128 mg, 40%). ¹H NMR (d⁶ DMSO): δ 11.05 (s, 1H), 8.08 (s, 1H), 7.80 (s, 1H), 6.70 (dd, 1H, J = 11.1 & 17.7 Hz), 5.79 (d, 1H, J = 17.7 Hz), 5.22 (d, 1H, J = 11.1 Hz), 3.57 (s, 2H). MS (-ve APCI): 159 (100, M-H).

Example of Method F:

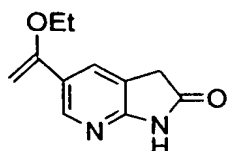


5-ethyl-7-azaoxindole

a) 5-ethyl-7-azaoxindole

To a stirred mixture of 5-vinyl-7-azaoxindole (32 mg, 0.2 mmol) in ethanol (10 ml) was added 10% palladium on carbon (10 mol %). Hydrogen (40 psi) was applied and the mixture was stirred at room temperature for 3 hours. The reaction mixture was filtered through celite and washed with ethanol. Evaporation of the filtrate under vacuum yielded 5-ethyl-7-azaoxindole as a peach solid (31 mg, 95.7%). ¹H NMR (d⁶ DMSO): δ 10.92 (s, 1H), 7.91 (s, 1H), 7.47 (s, 1H), 3.54 (s, 2H), 2.56 (q, 2H, J = 7.4 Hz), 1.17 (t, 3H, J = 7.4 Hz). MS (-ve APCI): 161 (100, M-H).

Example of Method G:

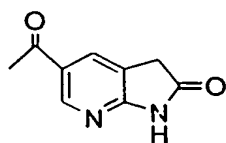


5-(1-ethoxyvinyl)-7-azaoxindole

5 a) 5-(1-ethoxyvinyl)-7-azaoxindole

To a stirred mixture of 5-bromo-7-azaoxindole (112 mg, 0.5 mmol) in acetonitrile (4 ml) were added tributyl(1-ethoxyvinyl)tin (228 mg, 0.6 mmol), tetraethylammonium chloride (174 mg, 1 mmol), and dichlorobis(triphenylphosphine)palladium(II) (37 mg, 0.05 mmol) under N₂ atmosphere. The reaction mixture was heated to reflux at 95 °C for 18 hours. The reaction mixture was diluted with diethyl ether (50 ml) and washed with 2 M potassium fluoride solution (10 ml). The aqueous layer was thoroughly extracted with diethyl ether. The combined organic layers were dried over anhydrous MgSO₄, filtered and evaporated under vacuum to give crude product. Trituation of the crude product with diethyl ether yielded 5-(1-ethoxyvinyl)-7-azaoxindole as a yellow solid (59.5 mg, 55.4%). ¹H NMR (d⁶ DMSO): δ 11.09 (s, 1H), 8.32 (s, 1H), 7.76 (s, 1H), 4.71 (s, 1H), 4.27 (s, 1H), 3.90 (q, 2H, J = 7 Hz), 3.58 (s, 2H), 1.36 (t, 3H, J = 7 Hz). MS (-ve APCI): 203 (38, M-H).

Example of Method H:



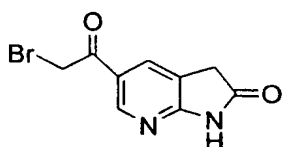
5-acetyl-7-azaoxindole

a) 5-acetyl-7-azaoxindole

To a stirred mixture of 5-bromo-7-azaoxindole (1 g, 4.69 mmol) in acetonitrile (30 ml) were added tributyl(1-ethoxyvinyl)tin (1.8 g, 4.93 mmol),

tetraethylammonium chloride (778 mg, 4.69 mmol), and dichlorobis(triphenylphosphine)palladium(II) (165 mg, 0.23 mmol) under N₂ atmosphere. The reaction mixture was heated to reflux at 95 °C for 15 hours. The reaction mixture was diluted with diethyl ether (100 ml) and washed with 2 M potassium fluoride solution (10 ml). The aqueous layer was thoroughly extracted with diethyl ether. The combined organic layers were dried over anhydrous MgSO₄, filtered and evaporated under vacuum to give crude product. Tritiation of the crude product with diethyl ether yielded 5-(1-ethoxyvinyl)-7-azaaxindole as a yellow solid (200 mg, 20.9%). The filtrate was evaporated to small volume and was purified by silica gel column chromatography, eluted with a gradient of ether in hexanes, to give 5-(methylcarbonyl)-7-azaaxindole as a yellow solid (203 mg, 24.5%). ¹H NMR (d₆-DMSO): δ 11.45 (s, 1H), 8.76 (s, 1H), 8.01 (s, 1H), 3.63 (s, 2H), 2.52 (s, 3H). MS (-ve APCI): 175 (100, M-H).

Example of Method I:

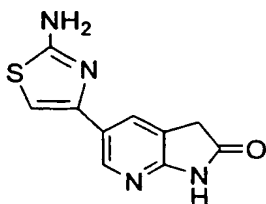


5-Bromomethylcarbonyl-7-azaaxindole

a) 5-(bromomethylcarbonyl)-7-azaaxindole

To a stirred solution of 5-(1-ethoxyvinyl)-7-azaaxindole (104 mg, 0.51 mmol) in tetrahydrofuran (12 ml) and water (1.2 ml) was added *N*-bromosuccinimide (109 mg, 0.61 mmol). The reaction mixture was stirred at room temperature for 5 min. The reaction mixture was diluted with ethyl acetate (50 ml), dried over anhydrous MgSO₄, filtered and evaporated under vacuum to give crude product. Tritiation of the crude product with dichloromethane/methanol yielded 5-(bromomethylcarbonyl)-7-azaaxindole as a tan solid (90.9 mg, 70%). ¹H NMR (d₆ DMSO): δ 11.53 (s, 1H), 8.82 (s, 1H), 8.05 (s, 1H), 4.90 (s, 2H), 3.67 (s, 2H). MS (-ve APCI): 255 (28, M⁺).

Example of Method J:

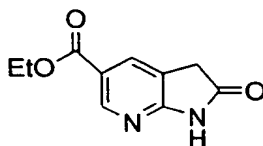


5-(2'-aminothiazole)-7-azaoxindole

a) 5-(2'-aminothiazole)-7-azaoxindole

To a stirred solution of 5-(bromomethylcarbonyl)-7-azaoxindole (90 mg, 0.35 mmol) in tetrahydrofuran (6 ml) was added thiourea (27 mg, 0.35 mmol). The reaction mixture was heated at 100 °C for 18 hours in sealed tube. The reaction mixture was filtered and washed with ethyl acetate. The filtrate was evaporated under vacuum to give crude product which was purified by preparative thin layer chromatography to give 5-(aminothiazole)-7-azaoxindole as a tan solid (32.2 mg, 39.3%). ¹H NMR (d⁶ DMSO): δ 11.18 (s, 1H), 8.48 (s, 1H), 8.26 (s, 1H), 8.05 (s, 1H), 7.93 (s, 1H), 7.60 (s, 1H), 7.10 (s, 1H), 3.63 (s, 2H). MS (-ve-APCI): 231 (7, M-H).

Example of Method K:



5-carboethoxy-7-azaoxindole

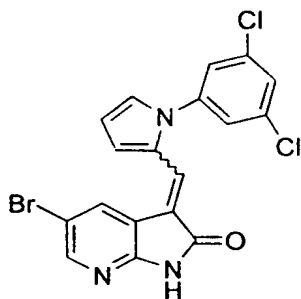
a) 5-carboethoxy-7-azaoxindole

To a mixture of 5-bromo-7-azaoxindole (213 mg, 1 mmol) in dimethylsulfoxide (1 ml) and ethanol (5 ml) in Parr bomb were added triethylamine (0.31 ml, 2.25 mmol), palladium acetate (33.7 mg, 0.15 mmol), and

1,4-(bisdiphenylphosphino)propane (61.9 mg, 0.15 mmol). Carbon monoxide gas (40 atm) was applied and the reaction mixture was heated at 95 °C for 18 hours with vigorously stirring. The reaction mixture was diluted with diethyl ether (50 ml) and washed with water (10 ml). The aqueous layer was thoroughly extracted with diethyl ether. The combined organic layers were dried over anhydrous MgSO₄, filtered and evaporated under vacuum to give crude product. Trituration of the crude product with methanol yielded 5-(carboethoxy)-7-azaoxindole as a tan solid (53 mg, 25.7%). ¹H NMR (d⁶ DMSO): δ 11.39 (s, 1H), 8.62 (s, 1H), 7.95 (s, 1H), 4.27 (q, 2H, J = 7 Hz), 3.59 (s, 2H), 1.28 (t, 3H, J = 7 Hz). MS (-ve APCI): 205 (4, M-H).

Methods for the synthesis of compounds of formula (I):

Example of Method AA:



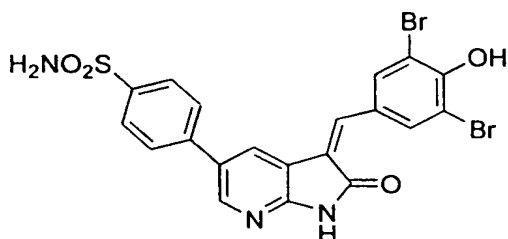
Example 20: 5-Bromo-3-[1-(3,5-dichlorophenyl)-1H-pyrrol-2-ylmethylene]-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one

The following reagents were combined under N₂ at room temperature: 5-Bromo-7-aza-oxindole (0.020 g, 0.93 mmol), 1-(3,5-dichlorophenyl)-pyrrole-2-carboxaldehyde (0.0225 g, 0.93 mmol), toluene (1 mL), and 4-methylmorpholine (1 drop). The reaction temperature was increased to 110 °C for 6 hours. A solid had precipitated from the reaction mixture. The reaction was cooled to room temperature and the solid was collected by filtration, washed with toluene (3 mL)

and Et₂O (5 mL). The solid was dried in vacuo to afford the title compound as a yellow solid. (0.026 g, 64% yield). ¹H NMR (d⁶ DMSO) δ 6.60 (m, 1H); 7.20 (s, 1H); 7.26 (s, 1H); 7.60 (m, 3H); 7.75 (s, 1H); 8.21 (d, 2H); 11.31 (bs, 1H). Electrospray MS: 434, 436, 438 (MH⁺).

5

Example of Method BB:



10

Example 9: 4-[3-(3,5-Dibromo-4-hydroxy-benzylidene)-2-Oxo-2,3-dihydro-1H-pyrrolo [2,3-b] pyridin-5-yl] benzenesulfonamide.

15

A mixture of 0.075 g (0.26 mmol) of 5-(4-benzene sulfonamide)-7-aza-oxindole and 0.087 g (0.31 mmol) of 3,5-dibromo-4-hydroxybenzaldehyde was stirred in 1 ml of HOAc. 50 ml of concentrated HCl was added and the mixture was heated to 80°C for 42 hrs. After cooling to ambient temperature the reaction mixture was diluted with EtOAc. The solid was collected by vacuum filtration and washed with EtOAc and Et₂O to yield 4-[3-(3, 5-Dibromo-4-hydroxy-benzylidene)-2-Oxo-2, 3-dihydro-1H-pyrrolo [2, 3-b] pyridin-5-yl] benzenesulfonamide as a yellow solid (0.103 g, 72%): ¹H NMR (DMSO-d₆): δ 7.39 (s, 2H), 7.89 (s, 4H), 7.94 (s, 1H), 8.39 (d, J = 2 Hz, 1H), 8.48 (d, J = 2 Hz, 1H), 8.75 (s, 2H), 11.45 (s, 1H); ESI-MS: m/z 550 (m-H)⁺.

20

25

The following Examples were obtained using the above described reaction schemes, routes and synthesis strategies, but with the appropriate reagent, reaction conditions and reactant substitutions that will be readily realized by those of ordinary skill in this art, without the exercise of undue experimentation.

Example 1: 3-(3,5-Dibromo-4-hydroxy-benzylidene)-5-thiophen-2-yl-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one

¹H NMR (d⁶ DMSO): 11.46 (s, 1H), 8.81 (s, 2H), 8.44 (s, 1H), 8.32 (s, 1H), 7.99 (s, 1H), 7.60 (d, 1H, J = 5.1 Hz), 7.54 (d, 1H, J = 3.0 Hz), 7.20 (dd, 1H, J = 3.0, 5.1 Hz).

MS (-ve APCI): 480 (12, M+2), 479 (55, M+1), 478 (20, M⁺), 477 (100).

Example 2: 3-(3,5-Dibromo-4-hydroxy-benzylidene)-5-phenyl-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one

¹H NMR (d⁶ DMSO): 11.42 (s, 1H), 8.80 (s, 2H), 8.44 (s, 1H), 8.37 (s, 1H), 7.99 (s, 1H), 7.73 (d, 2H, J = 7.3 Hz), 7.52 (t, 2H, J = 7.3 Hz), 7.41 (t, 1H, J = 7.3 Hz).

MS (-ve ES): 470 (10, M⁺), 471 (45, M-H).

Example 3: 3-(3,5-Dibromo-4-hydroxy-benzylidene)-5-vinyl-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one

¹H NMR (d⁶ DMSO): 11.36 (s, 1H), 8.76 (s, 2H), 8.26 (s, 1H), 8.13 (s, 1H), 7.86 (s, 1H), 6.77 (dd, 1H, J = 10.6, 17.8), 5.87 (d, 1H, J = 17.8 Hz), 5.30 (d, 1H, J = 10.6 Hz).

MS (-ve ES): 423 (22, M+1), 422 (10, M⁺), 421 (60), 198 (40), 163 (95), 162 (100).

Example 4: 5-Acetyl-3-(3,5-dibromo-4-hydroxy-benzylidene)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one

¹H NMR (d⁶ DMSO): 11.77 (s, 1H), 8.81 (s, 2H), 8.79 (s, 1H), 8.52 (s, 1H), 8.08 (s, 1H), 8.02 (s, 1H), 2.62 (s, 3H).

MS (-ve ES): 439 (22, M+1), 438 (8, M⁺), 437 (38), 279 (100).

Example 7: 3-(3,5-Dibromo-4-hydroxy-benzylidene)-5-furan-2-yl-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one

¹H NMR (d⁶ DMSO): 11.46 (s, 1H), 8.82 (s, 1H), 8.78 (s, 2H), 8.45 (s, 1H), 8.27 (s, 1H), 7.92 (s, 1H), 7.59 (m, 1H), 6.93 (d, 1H, J = 3.3 Hz), 6.40 (d, 1H, J = 3.3 Hz).

MS (-ve ES): 463 (28, M+1), 462 (26, M⁺), 461 (100, M-H), 459 (55).

Example 8: 3-(3,5-Dibromo-4-hydroxy-benzylidene)-5-thiophen-3-yl-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one

¹H NMR (DMSO-d₆) δ 7.57 (d, 1H, J=5.2 Hz); 7.68 (m, 1H); 7.84 (s, 1H); 7.87 (s, 1H); 8.35 (s, 1H); 8.47 (s, 1H); 8.73 (s, 2H); 11.35 (s, 1H).

Electrospray MS (ES+) 476.6, 478.7, 480.7; (ES-) 474.8, 476.7, 478.7.

Example 9: 4-[3-(3, 5-Dibromo-4-hydroxy-benzylidene)-2-Oxo-2,3-dihydro-1H-pyrrolo [2, 3-b] pyridin-5-yl] benzenesulfonamide.

A mixture of 0.075 g (0.26 mmol) of 5-(4-benzene sulfonamide)-7-aza-oxindole and 0.087 g (0.31 mmol) of 3,5-dibromo-4-hydroxybenzaldehyde was stirred in 1 ml of HOAc. 50 ml of concentrated HCl was added and the mixture was heated to 80°C for 42 hrs. After cooling to ambient temperature the reaction mixture was diluted with EtOAc. The solid was collected by vacuum filtration and washed with EtOAc and Et₂O to yield 4-[3-(3, 5-Dibromo-4-hydroxy-benzylidene)-2-Oxo-2, 3-dihydro-1H-pyrrolo [2, 3-b] pyridin-5-yl] benzenesulfonamide as a yellow solid (0.103 g, 72%): ¹H NMR (DMSO-d₆): δ 7.39 (s, 2H), 7.89 (s, 4H), 7.94 (s, 1H),

8.39 (d, $J = 2$ Hz, 1H), 8.48 (d, $J = 2$ Hz, 1H), 8.75 (s, 2H), 11.45 (s, 1H); ESI-MS: m/z 550 (m-H)⁻.

Example 12: 3-(3,5-Dibromo-4-hydroxy-benzylidene)-2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid benzyl ester

¹H NMR (d⁶ DMSO): 11.80 (s, 1H), 8.84 (s, 2H), 8.76 (d, 1H, $J = 1.8$ Hz), 8.53 (d, 1H, $J = 1.8$ Hz), 8.07 (s, 1H), 7.36-7.54 (m, 6H), 5.42 (s, 2H).

MS (-ve APCI): 530 (4, M⁺), 396 (24), 394 (100).

Example 13: Isopropyl-[(3,5-dibromo-4-hydroxyphenyl)methylidene]-2-oxo-1,2-dihydro-3H-pyrrolo[2,3-b]pyridine-5-carboxylate

¹H NMR (d⁶ DMSO): 11.74 (s, 1H), 8.71 (s, 1H), 8.33 (s, 1H), 8.03 (s, 2H), 7.75 (s, 1H), 5.14 (m, 1H, $J = 6.2$ Hz), 1.32 (d, 6H, $J = 6.2$ Hz).

MS (-ve APCI): 482 (5, M⁺), 441 (35), 439 (100), 397 (52), 395 (80).

Example 16: 5-(2-Amino-thiazol-4-yl)-3-(3,5-dibromo-4-hydroxy-benzylidene)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one

¹H NMR (d⁶ DMSO): 11.44 (s, 1H), 8.73 (s, 2H), 8.47 (s, 1H), 8.34 (s, 1H), 8.24 (s, 1H), 8.03 (s, 1H), 7.83 (s, 1H), 7.23 (s, 1H), 7.01 (s, 1H).

MS (-ve APCI): 495 (5, M+1), 415 (16), 198 (25), 165 (50), 163 (100).

Example 20: 5-Bromo-3-[1-(3,5-dichlorophenyl)-1H-pyrrol-2-ylmethylene]-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one

The following reagents were combined under N₂ at room temperature: 5-Bromo-7-aza-oxindole (0.020 g, 0.93 mmol), 1-(3,5-dichlorophenyl)-pyrrole-2-

carboxaldehyde (0.0225 g, 0.93 mmol), toluene (1 mL), and 4-methylmorpholine (1 drop). The reaction temperature was increased to 110 °C for 6 hours. A solid had precipitated from the reaction mixture. The reaction was cooled to room temperature and the solid was collected by filtration, washed with toluene (3 mL) and Et₂O (5 mL). The solid was dried in vacuo to afford the title compound as a yellow solid. (0.026 g, 64% yield). ¹H NMR (d⁶ DMSO) δ 6.60 (m, 1H); 7.20 (s, 1H); 7.26 (s, 1H); 7.60 (m, 3H); 7.75 (s, 1H); 8.21 (d, 2H); 11.31 (bs, 1H). Electrospray MS: 434, 436, 438 (MH⁺).

Example 22: 3-(3,5-Dibromo-4-hydroxybenzylidene)-5-ethyl-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one

¹H NMR (d⁶ DMSO): 11.26 (s, 1H), 8.78 (s, 2H), 7.98 (s, 1H), 7.92 (s, 1H), 7.82 (s, 1H), 2.62 (q, 2H, J = 7.6 Hz), 1.24 (t, 3H, J = 7.6 Hz).

MS (-ve APCI): 161 (100, M-H).

MS (+ve APCI): 425 (18, M+1), 423 (16), 141 (61), 109 (100).

Example 25: 3-(3,5-Dibromo-4-hydroxy-benzylidene)-2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid ethyl ester

¹H NMR (d⁶ DMSO): 11.67 (s, 1H), 8.66 (s, 1H), 8.30 (s, 1H), 7.97 (s, 2H), 7.69 (s, 1H), 4.24 (q, 2H, J = 7.2 Hz), 1.28 (t, 3H, J = 7.2 Hz).

MS (-ve APCI): 468 (8, M⁺), 439 (20), 394 (8), 326 (58), 288 (100).

Example 27: 3-(3-Bromo-4-hydroxy-5-(2'-methoxyphenyl)-benzylidene)-5-bromo-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one

¹H NMR (DMSO-d₆) δ 3.80 (s, 3H); 7.04 (m, 1H); 7.17 (d, 1H, J=8.40 Hz); 7.24 (m, 1H); 7.45 (d, 1H, J=7.5 Hz); 7.95 (s, 1H); 8.11 (d, 1H, J=2.1 Hz); 8.19 (d, 1H, J=2.1 Hz); 8.25 (d, 1H, J=1.8 Hz); 8.96 (d, 1H, J=2.1 Hz); 11.42 (bs, 1H).

APCI MS: 499 (60%), 501 (100%), 503 (60%), (M-H).

Example 28: 5-Bromo-3-[(3,5-dibromo-4-hydroxyphenyl)methylidene]-1H-pyrrolo[2,3-b]pyridin-2-one

¹H NMR (d⁶ DMSO) δ 11.47 (s, 1H), 8.73 (s, 2H), 8.21 (s, 1H), 8.19 (s, 1H), 7.8 (s, 1H).

MS (AP-ve) 475 (100) (M-H).

Example 29: 5-Bromo-3-[(3-phenoxyphenyl)methylidene]-1H-pyrrolo[2,3-b]pyridin-2-one

¹H NMR (DMSO-d₆) δ 7.04 (d, 2H, J=6.30 Hz); 7.15 (m, 2H); 7.39 (m, 2H); 7.50 (dd, 1H, J=6.0 Hz); 7.97 (s, 1H); 8.02 (d, 1H, J=5.70 Hz); 8.16 (m, 2H); 8.29 (d, 1H, J=1.50 Hz); 11.41 (bs, 1H).

Electrospray MS (ES+) 393.3, 395.2

Example 30: 6-chloro-3-[(3,5-dibromo-4-hydroxyphenyl)methylidene]-1H-pyrrolo[2,3-b]pyridin-2-one

¹H NMR (DMSO-d₆) (E-isomer): δ 7.09 (d, 1H, J = 8.0 Hz), 7.68 (s, 1 H), 7.78 (d, 1H, J = 8.0 Hz), 7.95 (s, 2H), 11.51 (s, 1H). (Z-isomer): δ 7.17 (d, 1H, J = 8.0 Hz), 7.85 (s, 1 H), 8.00 (d, 1H, J = 7.9 Hz), 8.77 (s, 2H), 11.55 (s, 1H).

MS (+ve AP) 429 (45%), 431 (100), 433 (68%), 435 (10%) (M+H).

Anal. Calcd. for C₁₄H₇Br₂ClN₂O₂: C, 39.18; H, 2.26; N, 5.71; Br, 32.58; Cl, 7.23.
Found: C, 38.89; H, 2.16; N, 5.85; Br, 32.46; Cl, 7.20.

Example 35: 5-bromo-3-[(Z)-(3,5-dimethyl-1H-pyrrol-2-yl)methylidene]-1H-pyrrolo[2,3-b]pyridin-2-one

¹H NMR (DMSO-d₆) δ 2.35 (s, 3H); 2.37 (s, 3H); 6.11 (s, 1H); 7.80 (s, 1H); 8.08 (d, 1H, J=1.5 Hz); 8.41 (d, 1H, J=1.5 Hz); 10.65 (bs, 1H); 13.23 (bs, 1H).

APCI MS 319 (MH⁺)

Example 37: 3-[2-Furylmethylidene]-5-(3-thienyl)-1H-pyrrolo[2,3-b]pyridin-2-one

¹H NMR (DMSO-d₆) δ 6.88 (s, 1H); 7.40 (d, 1H, J=3.6 Hz); 7.54 (s, 1H); 7.64 (d, 1H, J=5.1 Hz); 7.72 (m, 1H); 7.96 (s, 1H); 8.37 (s, 1H); 8.54 (s, 1H); 8.84 (s, 1H); 11.29 (s, 1H).

Electrospray MS (ES⁺) 295.2 (MH⁺)

Example 38: 3-(-4-[3-(dimethylamino)propoxy]phenylmethylidene)-5-(3-thienyl)-1H-pyrrolo[2,3-b]pyridin-2-one

¹H NMR (DMSO-d₆) δ 1.91 (m, 2H); 2.18 (s, 6H); 2.40 (m, 2H); 4.14 (m, 2H); 7.17 (d, 2H, J=8.7 Hz); 7.48 (d, 1H, J= 4.8 Hz); 7.69 (m, 1H); 7.79 (s, 2H); 7.83 (d, 2H, J=8.7 Hz); 8.19 (s, 1H); 8.50 (s, 1H); 11.30 (s, 1H),

Electrospray MS (ES⁺) 405 (MH⁺)

Example 41: 5-Bromo-3-[(4-hydroxy-3,5-diisopropylphenyl)methylidene]-1H-pyrrolo[2,3-b]pyridin-2-one

¹H NMR (DMSO-d₆) δ 1.22 (d, 12H); 3.42 (m, 2H); 7.43 (s, 2H); 7.80 (s, 1H); 8.06 (s, 1H); 8.24 (s, 1H); 9.11 (bs, 1H); 11.40 (bs, 1H).

Electrospray MS: 401 (70%); 403 (100%).

Example 42: 3-[(4-Hydroxy-2-methoxyphenyl)methylidene]-5-phenyl-1H-pyrrolo[2,3-b]pyridin-2-one

¹H NMR (DMSO-d₆) δ 3.81 (s, 3H); 6.51 (m, 2H); 7.32 (m, 1H); 7.42 (m, 2H); 7.53 (d, 2H, J=7.2 Hz); 7.68 (d, 1H, J= 8.0 Hz); 7.80 (s, 1H); 7.98 (s, 1H); 8.32 (s, 1H); 11.20 (s, 1H).

MS AP+ 344 (M+1); AP+ 328 (M-16+1); AP- 326 (M-16+1)

Example 45: 3-[(3,5-Dichloro-4-hydroxyphenyl)methylidene]-5-(2-furyl)-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one

¹H NMR (DMSO-d₆) δ 6.17 (m, 1H); 6.84 (d, 1H, J=3.30 Hz); 7.70 (s, 1H); 7.76 (s, 1H); 7.88 (s, 2H); 8.13 (d, 1H, J=1.50 Hz); 8.53 (d, 1H, J=1.80Hz); 11.41 (bs, 1H).

Electrospray MS (ES-) 371 (M-H)

Example 46: 3-[(3,5-Dimethyl-1H-pyrrol-2-yl)methylidene]-5-(2-furyl)-1H-pyrrolo[2,3-b]pyridin-2-one

¹H NMR (DMSO-d₆): δ 2.32 (s, 6H), 6.04 (s, 1H), 6.59 (m, 1H), 6.89 (d, J = 3 Hz, 1H), 7.73 (s, 1H), 7.75 (s, 1H), 8.33 (s, 1H), 8.37 (s, 1H), 11.44 (s, 1H), 13.23 (s, 1H)

ESI-MS: m/z 306 (m+H)⁺.

Example 47: 5-(2-Furyl)-3-[(4-hydroxy-2-methoxyphenyl)methylidene]-1H-pyrrolo[2,3-b]pyridin-2-one

¹H NMR (DMSO-d₆): δ 3.80 (s, 3H), 6.54 (m, 3H), 6.78 (d, J = 3 Hz, 1H), 7.62 (d, J = 8.9 Hz, 1H), 7.70 (s, 1H), 7.79 (s, 1H), 8.00 (s, 1H), 8.43 (d, J = 1.6 Hz, 1H), 10.34 (bs, 1H), 11.23 (s, 1H)

5 ESI-MS: *m/z* 335 (m+H)⁺.

UTILITY

10 Kinase signal transduction results in, among other responses, cell proliferation, differentiation and metabolism. Abnormal cell proliferation may result in a wide array of disorders and diseases, including the development of neoplasia such as carcinoma, sarcoma, leukemia, glioblastoma, hemangioma; psoriasis, arteriosclerosis, arthritis and diabetic retinopathy or other disorders related to uncontrolled angiogenesis and/or vasculogenesis.

15 The efficacy of compounds of the present invention as inhibitors of protein kinase activity can be evaluated and measured using pharmacological methods known in the art or as described in detail below based on similarly established methodologies.

20

Substrate phosphorylation assay examples:

A. cRaf1 Assay

25 Human cRaf1 tagged with poly histidine at the carboxyterminus was expressed in a baculovirus expression system and purified by Ni chelate affinity chromatography. Human MEK1 was expressed in *e. coli* as a fusion protein with Glutathione-S-transferase, and purified by glutathione sepharose affinity chromatography. Typically assays were performed in a final volume of 40 - 100 mL with and without inhibitors. Reactions contained cRaf1 (20 nM), MEK1 (100-
30 500 nM), [γ-³²P]ATP (10-20 mM), Mg²⁺ (10 mM), MOPS (50 mM, pH 7.5). Reactions were incubated at room temperature for periods of time ranging from 20-120 minutes. Inhibitors were diluted in 100% DMSO prior to addition to the

assay. Reactions were terminated with an equal volume of 0.5% phosphoric acid. MEK1 phosphorylation was detected by scintillation counting following collection of protein onto phosphocellulose filters.

5 B. Raf/MEK Cascade Assay

Human cRaf1 and MEK1 were purified as described above. A peptide substrate phosphorylated by MEK1 was used as the final phosphoryl group acceptor. The sequence of the peptide HTGFLTEYVATRWKK-OH was derived from the site in ERK2 that is phosphorylated by MEK1. Assay conditions were the same as those described above except for the following modifications. Reactions contained cRaf1 (1-5 nM), MEK1 (60 nM), and peptide (250 mM).

10 C. CDK1 and CDK2 Assay

Cyclin dependent protein kinase assays utilized the peptides Biotin-aminohexyl-AAKAKKTPKKAKK and Biotin-aminohexyl-ARRPMSPKKKA-NH₂ as phosphoryl group acceptors. CDK1 and CDK2 were both expressed utilizing a baculovirus expression system and were partially purified to comprise 20-80% of total protein, with no detectable competing reactions present. Typically, assays were performed by incubating either enzyme (0.2-10nM), with and without inhibitor, one of the two peptide substrates (1-10nM), [γ -³²P]ATP (1-20nM), and 10-20mM Mg²⁺ for periods of time generally within the range 10-120 minutes. Reactions were terminated with 0.2-2 volumes of either 20% acetic acid or 50-100mM EDTA buffered to pH 7 (substrate consumption < 20%). The buffer employed in enzyme assays was either 30mM HEPES 7.4 containing 0.15M NaCl and 5% DMSO, the buffer 50mM MOPS 7.0 containing 0.15M NaCl and 5% DMSO, or the buffer 100mM HEPES pH 7.5 containing 0.1mg/mL BSA and 5% DMSO. Inhibitors were diluted in 100% DMSO prior to addition into the assay. Detection of peptide phosphorylation was accomplished by scintillation counting following either collection of peptide onto phosphocellulose filters (for reactions stopped with acetic acid), collection of peptide in wells of 96 well plates coated with Streptavidin (Pierce) (reactions were stopped with EDTA), or addition of Avidin coated Scintillant impregnated beads (Scintillation Proximity Assays from

Amersham, reactions were stopped with EDTA). Counts detected by any of these methodologies minus the appropriate background (assays with additional 40mM EDTA or lacking peptide substrate) were assumed to be proportional to the reaction initial rates, and IC50s were determined by a least squares fit to the equation $CPM = V_{max} * (1 - ([I]/(K + [I]))) + nsb$, or -pIC50s were determined by a fit to the equation $CPM = nsb + (V_{max} - nsb) / (1 + (x/10^x - pIC50))$, where nsb are the background counts.

D. UL97

UL97 was produced as a GST fusion protein from a baculovirus vector expressed in sf9 cells as described by He (He et al., 1997). UL97 was assayed as a protein kinase using ^{32}P transfer from ATP to histone H2B with detection of radiolabeled histone bound to phosphocellulose. Assay mixes for testing inhibitors of UL97 activity contained 2 mM [$\gamma^{32}P$]-ATP, 15 mM histone H2B, 50 mM sodiumCHES, pH 9.5, 1 M NaCl, 2 mM dithiothreitol and 10 mM $MgCl_2$. Inhibitors were dissolved in diluted DMSO to give a final DMSO concentration in the reaction of 1% DMSO. After incubation at 20°C, the reactions were terminated by addition of 10 volumes of 75 mM phosphoric acid, 30 mM ATP, 1 mM EDTA, then were spotted onto phosphocellulose filters and washed four times with 75 mM phosphoric acid. Radioactivity was determined by liquid scintillation counting.

E. SRC/Lck Enzyme Assay

The peptide substrates used in Src and Lck assays were biotin-aminohexyl-EEIYGEF-NH₂ (Src) and biotin-aminohexyl-EAIYGVLFKKK-NH₂ (Lck). The src and lck proteins were purified to homogeneity from a baculovirus expression system and preactivated before adding to assay mixtures. The maximum activation was achieved by incubating concentrated enzyme (10-30 mM) on ice for 40 min in the presence of 1 mM ATP and 10 mM $MgCl_2$ in 100 mM HEPES, pH 7.5. The activated enzyme was diluted to 2 nM into an 50 mL reaction mixture containing 100 mM HEPES, pH 7.5, 5 mM ATP, 10 mM $MgCl_2$, 2 mM peptide, 0.05 mg/mL BSA, and an inhibitor at varying concentrations and with or without 8 mCi/mL [$\gamma^{33}P$]ATP dependent upon the method of analysis for the extent of

reaction. The controls were reactions in the presence (negative controls) or absence (positive controls) of 50 mM EDTA. Reactions were allowed to proceed for 30 min at room temperature and quenched with addition of EDTA to 50 mM in 220 mL. The extent of reactions was analyzed in one of the two ways: an Elisa-based and a radioactive isotope-based. The quenched samples (200 mL) were transferred to a neutravidin coated plate (Perice) and incubated at room temperature for 40 min to allow biotinylated peptide to bind to neutravidin. The unbound peptide and the rest of the solution was washed away using a plate washer. In the Elisa format, a 200 mL HRP-PY20 anti phosphotyrosine antibody conjugate solution was added. After incubation for about 30 min, the plate was washed to remove unbound antibody-HRP conjugate. An Elisa substrate, K-blue (Neogen), was added and the Elisa reaction quenched with Red-stop (Neogen) after 15 min. The plate was read at A_{625} in a plate reader. In the isotope-based format, the reactions had been performed in the presence of $[\gamma\text{-}^{33}\text{P}]\text{ATP}$. 200 mL Scintiverce DB was added to each well of the plate with bound biotin-peptide. The plate was sealed and counted in a micro-b-counter (Wallac). IC_{50} values were obtained by fitting raw data to $A_{625} \text{ (cpm)} = V_{\text{max}} * (1 - ([I]/(\text{IC}_{50} + [I]))) + b$, where b is background.

F. VEGFR-2 Tyrosine Kinase Assay

The peptide substrate used in the VEGFR-2 assay was biotin-aminohexyl-EEEEYFELVAKKKK-NH₂. The kinase domain of the enzyme was purified to homogeneity from a baculovirus expression system. The enzyme was preactivated on ice for 15 min in the presence of 100 μM ATP and 20 mM MgCl₂, and stored at -80°C until needed for assay. The activated enzyme was diluted to 0.4 nM into a 60 μl reaction containing 100 mM HEPES, pH 7.5, 5 μM ATP, 10 mM MgCl₂, 5 μM peptide, 0.1 mM DTT, 0.05 mg/ml BSA, and an inhibitor at varying concentrations. The controls were reactions in the presence (negative controls) or absence (positive controls) of 50 mM EDTA. Reactions were incubated for 30 min at room temperature, and then quenched by the addition of EDTA to 60 mM in 210 μl . The quenched samples (190 μl) were transferred to a neutravidin-coated plate (Pierce) and incubated at room temperature for 40 min to

allow biotinylated peptide to bind to the neutravidin. The unbound components of the reaction were removed by washing with a plate washer, then 200 μ L HRP-PY20 anti-phosphotyrosine antibody conjugate was added to each well. After incubation for 40 minutes, the plate was washed to remove any unbound antibody. A HRP substrate, K-blue (Neogen) was added and the reaction was quenched with Red Stop (Neogen) after 20 min. The absorbance of the wells was read at A_{650} in a plate reader. IC_{50} values were obtained by fitting raw data to $A_{650} = V_{MAX} * (1 - [I]/IC_{50} + [I])) + b$, where b is background.

G. Tie-2 Kinase Assay

Reaction: 0.5 μ M 3T68, 75 μ M ATP, 50 mM $MgCl_2$, 0.1 M Hepes, 0.1 mM DTT, 10 nM Tie-2. Enzyme reaction: 30 minutes at room temperature. Stop reaction with 100 μ L 0.15 M EDTA. Transfer 125 μ L to Neutravidin plate, incubate 30 minutes at room temperature. Wash plate with 300 μ L H_2O , 5 times. Add 150 μ L Eu-anti-pY (1:2000, kept at 4 $^{\circ}C$) and incubate for 30 minutes at room temperature. Wash plate with 300 μ L H_2O , 5 times. Add 150 μ L enhancement solution. Enzyme stability: stable for 24 hours at 250 nM in 6.25 mM DTT, 0.1 M Hepes, 0.1 mg/mL BSA, 4 $^{\circ}C$.

H. c-fms Assay

It is necessary to "preactivate" the enzyme to increase its' activity for the purpose of producing a good enzyme activity (signal) for the screening of compounds. C-fms is preactivated using the following conditions: 1mg/mL c-fms, 500 μ M ATP, 20mM $MgCl_2$, 50mM MOPS, pH 7.62 hour, room temperature incubation. Following the designated incubation time (2 hours), the enzyme is diluted to 75nM (~1:250) with room temperature 50mM MOPS, pH 7.6 and used in the Enzyme Assay described as follows. Substrate Solution (for screening): 50mM MOPS, pH 7.6, 25 μ M ATP, 20mM $MgCl_2$, 25 μ M EGFR peptide (EEEEYFELVAKKK). Enzyme assay (for screening): Enzyme assays are performed in round-bottom polystyrene 96-well plates. 45 μ L assay volume/well which includes 15 μ L of preactivated (diluted 1:250) c-fms enzyme solution, 15 μ L of substrate solution and 15 μ L of 6% DMSO (controls) or compound in 6%

DMSO. The final concentration of DMSO in the assay is 2%. Control wells, generally in A12-D12, include the addition of 15ul of 6% DMSO. Background wells, generally in E12-H12, include the addition of 15ul of 0.5M EDTA. Compounds in 6% DMSO are added to the round-bottomed 96-well plates. Enzyme solution and substrate solution are added using a Beckman Biomek 2000. The kinase (enzyme) assay is performed at room temperature for 30'. The reactions are stopped by the addition of 45ul 0.5% phosphoric acid, 60ul of this mix is transferred to 96-well MAPH (phosphocellulose) filter plates. The filter plates are placed on a vacuum manifold, filtered, and washed 3 times with 0.5% phosphoric acid. After washing, the plate bottoms are blotted on a paper towel, the bottom plastic (seal) piece is removed and the plate is placed in a Packard multiscreen adapter. 30ul of Optiphase supermix scintillation fluid is added to each well. The plates are sealed using a Packard plate sealer, placed in a Packard 96-well plate topcount scintillation counter for CPM determination. Data reduction is performed using the Microsoft Addin Robosage using the curve fitting function, $y = (V_{max} * x) / (k + x)$, and data reduction formula $100 * (U1 - C2) / (C1 - C2)$.

I. p38 kinase assay

The peptide substrate used in the p38 assay was biotin-IPTSPITTTYFFRRR-amide. The p38 and MEK6 proteins were purified to homogeneity from E.coli expression systems. The fusion proteins were tagged at the N-terminus with Glutathione-S-Transferase (GST). The maximum activation was achieved by incubating 20uL of a reaction mixture of 30nM MEK6 protein and 120nM p38 protein in the presence of 1.5μM peptide and 10mM $Mg(CH_3CO_2)_2$ in 100mM HEPES, pH 7.5, added to 15uL of a mixture of 1.5μM ATP with 0.08uCi [^{33}P]ATP, with or without 15uL of inhibitor in 6%DMSO. The controls were reactions in the presence (negative controls) or absence (positive controls) of 50 mM EDTA. Reactions were allowed to proceed for 60 min. at room temperature and quenched with addition of 50uL of 250mM EDTA and mixed with 150uL of Streptavidin SPA beads (Amersham) to 0.5mg/reaction. The Dynatech Microfluor white U-bottom plates were sealed and the beads were allowed to settle

overnight. The plates were counted in a Packard TopCount for 60 seconds. IC_{50} values were obtained by fitting raw data to $\%I = 100 \cdot (1 - (I - C2)/(C1 - C2))$, where I was CPM of background, $C1$ was positive control, and $C2$ was negative control.

- 5 The results shown in the following Tables (3-9) summarize representative data. The key listed below can be used for Tables 3 through 9.

Key	symbol	range
	+	$IC_{50} < 1 \mu M$
	++	IC_{50} from 1- 10 μM
	+++	IC_{50} from 10- 100 μM

- 10 **Table 3** illustrates the inhibitory activity of representative compounds of the present invention against raf kinase.

Table 3

Example	Raf
28	+
6	+
5	+
8	+
7	+
1	+
2	+
4	+
10	+
11	+
14	+

97

15	+
22	+
25	+
24	+
13	+
31	+
34	++
26	+
44	+
45	+

5 **Table 4** illustrates the inhibitory activity of representative compounds of the present invention against TIE2 kinase.

Table 4

Example	Tie 2
7	+
2	++
33	++
41	+
55	++
52	+

10

Table 5 illustrates the inhibitory activity of representative compounds of the present invention against CDK2.

Table 5

Example	CDK2
28	+
5	+
3	+
22	+
36	+

- 5 **Table 6** illustrates the inhibitory activity of representative compounds of the present invention against VEGFR Tyrosine Kinase.

Table 6

Example	VEGFR
28	++
3	+
4	++
21	++
14	+
20	++
15	+
16	+
27	++
32	++
35	+
36	+
37	+
38	+
39	+

99

43	+
48	++
53	++
49	+
54	+
55	+
52	+

Table 7 illustrates the inhibitory activity of representative compounds of the present invention against c-fms kinase.

5 **Table 7**

Example	c-fms
6	+
8	+
1	+
2	+
10	+
21	++
18	++
16	+
35	+
37	+
38	+
39	++
40	++
42	+
43	++
46	+
48	+

100

49	+
50	++
48	+
53	++
49	+
54	++
51	++
55	++
50	+
52	++

Table 8 illustrates the inhibitory activity of representative compounds of the present invention against p38 kinase.

5

Table 8

Example	P 38
28	+
11	++
27	+
22	+
30	+

Table 9 illustrates the inhibitory activity of representative compounds of the present invention against raf kinase.

10

Table 9

Example	Src
23	+

101

3	+
11	++
9	+
24	++

Cell-based assay examples:

5 As may be expected in light of specific inhibitory activity of these compounds against several kinases involved in growth regulation, angiogenesis, and inflammation, the compounds of this invention have properties which can be directly demonstrated in several cell-based assays. Representative assays are described below and representative data is summarized in Table 10.

10

A. MTT assay

The potency of compounds of the invention are tested for their ability to inhibit cell proliferation and cell viability. The metabolic conversion of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT, Sigma #M2128) to a reduced form is a commonly used measure of cellular viability. Following is the procedure:

15

Cells are maintained in 75cm² tissue culture flasks until ready for use. The cells are grown and plated for the assay in Dulbecco's modified Eagle's media containing 10% fetal bovine serum. For example, the following cell lines can be used: a) human foreskin fibroblasts (HFF), b) HT29 (human colon carcinoma cell line), c) MDA-MB-468 (human breast carcinoma cell line), d) RKO (human colon adenocarcinoma cell line), e) SW620 (human colon carcinoma cell line), f) A549 (human lung carcinoma cell line), and g) MIA PACA (human pancreatic carcinoma cell line). Cells are maintained at 37° C in 10% CO₂, 90% humidified air. Cells are plated in 96-well tissue culture plates at the densities listed below. 100μL of cell suspension is added to each well of the 96-well plate except the top row of the plate which contains no cells and serves as a reference for the spectrophotometer.

20

25

Cell line	Density
HFF	2500cells/well
HT29 cell lines	2500 cells/well
MDA-MB-468 cell line	5000 cells/well
SW620	4000 cells/well
MIA PACA	3000 cells/well
PC-3	4500 cells/well

Cells are incubated overnight in Dulbecco's modified Eagle's media containing 10% fetal bovine serum at 37° C in 10% CO₂, 90% humidified air prior to dosing. Cells are dosed in 10 sequential 3-fold dilutions starting at 30µM depending upon the solubility of the compound. Compounds with solubilities of less than 30µM are dosed at the highest soluble concentration. Stock solutions of compounds are made in 100% dimethyl sulfoxide (DMSO). Stock solutions are diluted in Dulbecco's modified Eagle's media containing 100µg/mL gentamicin and 0.3 to 0.6% DMSO at the twice the highest concentration to be placed on the cells. If compounds have been dissolved in DMSO the final concentration of DMSO on the cells is kept below 0.3%. 3-fold serial dilutions are performed on each compound to prepare 10 concentrations of the compound for dosing. 100µL of diluted compound is added to the 100µL of media currently on the dish. For each concentration of compound, 2-4 replicate wells are prepared.

Cells are returned to incubator and allowed to proliferate in the presence of compound for 72 hours before addition of MTT. MTT is prepared in phosphate buffered saline (Irvine Scientific #9240) at a concentration of 2mg/mL. 50µL per well of MTT solution is added to the 200µL of media to yield a final concentration of 0.4mg/mL and plates are returned to the incubator for 4 hours. After 4 hours incubation the media, compound and MTT mixture is aspirated from the plates and 100 µL of 100% DMSO is added to each well in addition to 25µL of Sorenson's Buffer (0.1M glycine, 0.1M NaCl, pH 10.5). Quantitation of metabolic reduction of MTT in each plate is performed by reading optical density at 570nm

wavelength on a Molecular Devices UVmax microplate reader. Growth inhibition curves and 50% inhibitory concentrations are determined using Microsoft Excel.

B. HUVEC MTT Assay Protocol

5 The following protocol may also be used to measure a compound's activity.

Cell culture: HUVEC (human umbilical vein endothelial cells) from Clonetics, cat. # CC-2519 (cryopreserved cells pooled from several donors). EGM-MV BulletKit, Clonetics cat. # CC-3125. Trypsin/EDTA, Clonetics cat. # CC-5012.

10 Fibronectin cellware from Becton Dickinson: 96-well plates, cat. # 40409. T-75 flasks, cat. # 40521. T-150 flasks, cat. # 40526 Plate HUVECs in complete Clonetics medium at 3500 cells/well in 96-well coated plates. (This is the number plated for up to a 3-day assay.) Place 100 μ l per well in the first 11 columns of the 96-well plate starting at the left side. Put 100 μ l of medium in the last column
15 on the right of each plate. Grow in 5% CO₂ incubator overnight.

Compound dosing: Compound stocks are made in DMSO at 10 mM. To prepare a 60 μ M starting solution, add 6 μ l of the 10 mM stock solution to 1 ml of medium. Prepare 1:3 serial dilutions in medium containing 0.6% DMSO for a total of 10
20 compound concentrations. We use deep well plates for this and do the dilutions with a Biohit 8-channel electronic pipetter. We typically do each compound dilution series in duplicate. Place 100 μ l of each dilution in the appropriate well on the cell culture plate. (After 100 μ l of compound solution is added to 100 μ l of cells, the highest final concentration on the plate will be 30 μ M.). Alternatively,
25 one can plate the cells in complete medium but then prepare 1X stocks (30 μ M and lower) of the compounds in the Clonetics medium containing only the supplied FBS, antibiotics, and hydrocortisone, plus 5 ng/ml VEGF. In this procedure the complete medium is aspirated from the cell culture plates and 200 μ l of each compound solution is added per well.

30 MTT detection: After selected time of exposure, add 50 μ l of MTT stock (2 mg/ml in PBS) and return to incubator. Plate multiple HUVEC plates for each compound

plate and then reading one set of plates each after 24, 48, and 72 hr. After 4 hr incubation, aspirate the medium and MTT. Add 100 μ l DMSO to each well and follow with 25 μ l Sorenson's buffer (0.1 M glycine, 0.1 M NaCl, pH 10.5). Read at 570 nm with automix on Molecular Devices Uvmax plate reader.

5

C. Cell-Based TNFa Release Inhibition Protocol

The potency of the compounds of the invention as inhibitors or release of soluble tumor necrosis factor α from stimulated monocytes in vitro is determined as follows; LPS/PMA solution for assay consisting of a) 4 μ L of 5 mg/mL LPS stock and b) 6 μ L of 10 mg/mL PMA stock are added to 500 μ L of medium (RPMI 1640 (Gibco) + 10% FBS + penicillin/streptomycin + L-glutamine). This solution is then 1:1000 (40 ng/mL and 120 ng/mL) for use later in the assay. Compounds (10 mM) are serially diluted 1:3 in DMSO. Compound dilutions (20 μ L) are added to a sterile round bottom 96 well plate (20 μ L:200 μ L total volume = 1:10 for final concentrations of 50 μ M for test compounds). MonoMac 6 cell suspension (130 μ L, 1.5×10^6 cells/mL) is then added to each well resulting in 2×10^5 cells/well. LPS/PMA (50 μ L) solution is then added to each well to begin stimulation (final concentrations of 10 ng/mL and 30 ng/mL respectively). The plate is incubated as 37 °C for 2 hours then spun at 1500 rpm for 3 minutes to pellet cells. The supernatant (120 μ L/well) is removed to a new round bottom 96 well plate and diluted 1:10 in PBS. Then, 20 μ L of the supernatant is transferred to a Cistron TNFa ELIZA plate and processed according to the manufacturer's instruction to quantitate levels of TNFa. Percent inhibition of TNFa release is calculated at each inhibitor concentration and the data were plotted using standard curve fitting programs. IC₅₀ values were determined from these curves.

10

15

20

25

Representative cell-based data are summarized in Table 10. Table 10 illustrates the inhibitory activity of compounds of the present invention in the HUVEC cell based assay and the TNFa release assay. Data for the cytotoxicity of representative compounds of the present invention are also shown for representative human tumor cell lines.

30

Table 10

Example #	MTT HT-29 (colon)	MTT MDA468 (breast)	HUVEC
1	++	++	ND
2	++	++	++
3	++	++	++
7	++	++	++
8	++	++	++
12	++	++	ND
13	++	++	ND
22	++	++	ND
24	++	++	ND
25	++	++	ND

Key	symbol	range
	+	IC ₅₀ < 1 μ M
	++	IC ₅₀ from 1- 50 μ M
	+++	IC ₅₀ from 50- 100 μ M
	ND	No data

IN VIVO ASSAYS

The following *in vivo* assay may be conducted to measure the effect of the claimed compounds upon *in vivo* tumor growth as a result of the compound's interaction with protein kinases. Unless otherwise specified, the following assays may be generally applied to measure the activity of a compound against many different tumor xenografts. To the extent that an assay, set forth below, refers to a specific tumor cell line, one skilled in the art would be able to adapt the disclosed protocol for use to measure the activity of the compounds in alternate tumor cell lines.

Anti-Tumor Studies: Animals

Mice are acquired from Taconic Farms and are maintained in Microisolator cages at $72 \pm 2^\circ\text{F}$ with a 12 hour light/dark cycle. Animals are housed at 4 mice per cage (28 x 17 x 12 cm) and are given food and water ad libitum. Animals are numbered through the use of an ear punch or tail tattoo. All animal handling is done in a laminar flow hood.

Tumor implantation

The tumor cell lines used for the protein kinase project are the colon lines SW620, RKO, HT-29. Tumors are initiated by subcutaneous injection of a cell suspension into the right flank of each mouse. The inoculum consists of 2×10^6 cells/mouse/ 0.2 ml in PBS:matrigel (1:1).

Cell growth

SW620, available from the American Type Culture Collection, are grown in media consisting of RPMI 1640 with fetal bovine serum (10%), sodium pyruvate (1.0 mM) and glutamine (2.0 mM). Cells are incubated at 37°C in 5% CO_2 . Cells are harvested with trypsin (0.05%), centrifuged, and resuspended in PBS:matrigel (1:1) at 1×10^7 cell/ml.

Tumor measurement

Solid tumors are measured by caliper measurement through the skin. Caliper measurements are typically made twice weekly. Tumor weight is calculated using the equation $(\text{length} \times \text{width}^2 / 2) = \text{mg tumor weight}$.

5 **Body weight measurement**

Mice are weighed twice weekly at the time of tumor measurement.

Compound Preparation

10 Compounds are prepared in a vehicle consisting of DMSO, Cremophore and PBS.

Experimental therapy

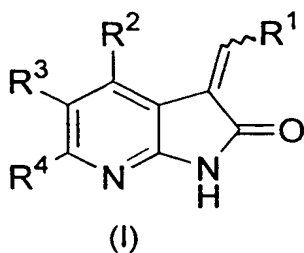
15 Drug therapy begins when the average tumor size is approximately 40-50 mg, which usually is day 7 after implant. The dose schedule consists of one dose/day for 5 consecutive days. Drugs are administered at 3 or 4 dose-levels based upon the previously-determined maximally tolerated dose. A vehicle control group is also included. Drugs may be administered by either i.v., i.p., s.c., or oral (p.o.) transdermal routes or other alternative routes. Drugs may be administered via tail vein infusion. The injection volume administered for each mouse is usually
20 0.01-0.02 mL/g of body weight. In the case of i.v. injections and tail vein infusion animals are restrained in a Broome restrainer during handling. Animal are fasted overnight prior to p.o. dosing. The duration of each experiment is typically 28 days from tumor implant.

25 While the invention has been described and illustrated with reference to certain preferred embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the preferred dosages as set forth herein above may be applicable as a
30 consequence of variations in the responsiveness of the mammal being treated for cancer conditions, or for other indications for the compounds of the invention indicated above. Likewise, the specific pharmacologic responses observed may

5 vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be limited only by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

Claims

1. A compound of formula (I)



wherein:

- 10 R^1 is Het, aryl, or biaryl with said Het, aryl, or biaryl being optionally substituted by one to four substituents selected from the group consisting of R^5 , $C(O)R^5$, $C(O)OR^5$, and OR^5 , where Het and R^5 are as defined below;

- 15 R^2 is H, Het, fused Het, aryl, C_{1-12} aliphatic, -CN, -NO₂, halogen, -OR⁵, -SR⁵, -S(O)R⁵, -NR⁵R⁷, -NR⁵COR⁵, -NR⁵CO₂R⁵, -NR⁵CONR⁵R⁷, -NR⁵SO₂R⁵, -NR⁵C(NR⁵)NHR⁵, -COR⁵, -CO₂R⁵, -CONR⁵R⁷, -SO₂NR⁵R⁷, -OCONR⁵R⁷, or -C(NR⁵)NR⁵R⁷, where said C_{1-12} aliphatic optionally bears one or two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, -S(O₂)-, and -N(R⁵)-, and wherein said Het, fused Het, aryl or C_{1-12} aliphatic are optionally substituted by one to three of R^5 , and where Het, fused Het, R^5 and R^7 are as defined below;
- 20

- 25 R^3 is H, Het, fused Het, aryl, C_{1-12} aliphatic, CN, NO₂, halogen, -OR⁵, -SR⁵, -S(O)R⁵, -NR⁵R⁷, -NR⁵COR⁵, -NR⁵CO₂R⁵, -NR⁵CONR⁵R⁷, -NR⁵SO₂R⁵, -NR⁵C(NR⁵)NHR⁵, -COR⁵, -CO₂R⁵, -CONR⁵R⁷, -SO₂NR⁵R⁷, aryl-SO₂NR⁵R⁷, -OCONR⁵R⁷, or -C(NR⁵)NR⁵R⁷, where said C_{1-12} aliphatic optionally bears one to two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-,

-S-, -S(O)-, -S(O₂)-, and -N(R⁵)-, where said Het, aryl or C₁₋₁₂ aliphatic are optionally substituted by one to three of R⁵, and where Het, fused Het, R⁵ and R⁷ are as defined below;

5 R⁴ is H, Het, fused Het, aryl, C₁₋₁₂ aliphatic, -CN, -NO₂, halogen, -OR⁵, -SR⁵,
 -S(O)R⁵, -NR⁵R⁷, -NR⁵COR⁵, -NR⁵CO₂R⁵, -NR⁵CONR⁵R⁷, -NR⁵SO₂R⁵,
 -NR⁵C(NR⁵)NHR⁵, -COR⁵, -CO₂R⁵, -CONR⁵R⁷, -SO₂NR⁵R⁷, -OCONR⁵R⁷, or
 -C(NR⁵)NR⁵R⁷, where said C₁₋₁₂ aliphatic optionally bears one or two aliphatic
 10 chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-,
 -S(O₂)-, and -N(R⁵)-, and wherein said Het, fused Het, aryl or C₁₋₁₂ aliphatic are
 optionally substituted by one to three of R⁵, and where Het, fused Het, R⁵ and R⁷
 are as defined below;

15 R⁵ is H, Het, aryl, halogen, or C₁₋₁₂ aliphatic, where said C₁₋₁₂ aliphatic optionally
 bears one to two aliphatic chain insertions selected from the group consisting of
 -O-, -S-, -S(O)-, -S(O₂)-, and -N(R⁶)-, where said C₁₋₁₂ aliphatic, aryl, or Het is
 optionally substituted by one to four of halogen, another Het or substituted Het,
 aryl or substituted aryl, -CN, -NO₂, -R⁶, -SR⁶, -OR⁶, -N(R⁶)₂, -S(O)R⁶, -SO₂R⁶,
 -SO₂N(R⁶)₂, NR⁶COR⁶, -NR⁶CON(R⁶)₂, -NR⁶(NR⁶)NHR⁶, -CO₂R⁶, -CON(R⁶)₂,
 20 -NR⁶SO₂R⁶, -OCON(R⁶)₂, or -NR⁶CO₂R⁶, where substituted Het and substituted
 aryl bear substituents that are any of -CN, -NO₂, -R⁶, -SR⁶, -OR⁶, -N(R⁶)₂,
 -S(O)R⁶, -SO₂R⁶, -SO₂N(R⁶)₂, NR⁶COR⁶, -NR⁶CON(R⁶)₂, -NR⁶(NR⁶)NHR⁶,
 -CO₂R⁶, -CON(R⁶)₂, -NR⁶SO₂R⁶, -OCON(R⁶)₂, or -NR⁶CO₂R⁶ and where Het
 and R⁶ are as defined below;

25 R⁶ is H, C₁₋₁₂ aliphatic, Het or aryl, where said C₁₋₁₂ aliphatic, Het or aryl is
 optionally substituted by one to three of halogen or OH, and where Het is as
 defined below;

30 R⁷ is H or R⁵;

Het is a five to ten membered saturated or unsaturated heterocyclic ring selected from the group consisting of acridine, benzimidazole, benzofuran, benzothiophene, benzoxazole, benzthiazole, carbazole, cinnoline, dioxin, dioxane, dioxalane, dithiane, dithiazine, dithiazole, dithiolane, furan, imidazole, imidazoline, imidazolidine, indole, indoline, indolizine, indazole, isoindole, isoquinoline, isoxazole, isothiazole, morpholine, naphthyridine, oxazole, oxadiazole, oxathiazole, oxathiazolidine, oxazine, oxadiazine, phenazine, phenothiazine, phenoxazine, phthalazine, piperazine, piperidine, pteridine, purine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrroline, quinoline, quinoxaline, quinazoline, quinolizine, tetrahydrofuran, tetrazine, tetrazole, thiophene, thiadiazine, thiadiazole, thiatriazole, thiazine, thiazole, thiomorpholine, thianaphthalene, thiopyran, triazine, triazole, and trithiane;

fused Het is where R^2 and R^3 or where R^3 and R^4 are optionally joined to form a fused ring selected from the group consisting of 5-10 membered aryl rings, 5-10 membered saturated heteroaryl rings or 5-10 membered unsaturated heterocyclyl rings, said heteroaryl or said heterocyclyl rings having one to three heteratoms where zero to three of said heteratoms are N and zero to one of said heteratoms are O or S and where said fused ring is optionally substituted by one to three of R^5 , where R^5 is defined above;

and the pharmaceutically acceptable salts, biohydrolyzable esters, biohydrolyzable amides, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, solvates, hydrates, affinity reagents or prodrugs of (I) as defined above.

2. A compound of formula (I) as claimed in claim 1 wherein:

R^1 is Het, aryl, or biaryl with said Het, aryl, or biaryl being optionally substituted by one to four substituents selected from the group consisting of R^5 , $C(O)R^5$, $C(O)OR^5$, and OR^5 , where Het and R^5 are as defined below;

R^2 is H, Het, fused Het, aryl, C_{1-6} aliphatic, -CN, -NO₂, halogen, -OR⁵, -SR⁵, -S(O)R⁵, -NR⁵R⁷, -NR⁵COR⁵, -NR⁵CO₂R⁵, -NR⁵CONR⁵R⁷, -NR⁵SO₂R⁵, -NR⁵C(NR⁵)NHR⁵, -COR⁵, -CO₂R⁵, -CONR⁵R⁷, -SO₂NR⁵R⁷, -OCONR⁵R⁷, or -C(NR⁵)NR⁵R⁷, where said C_{1-6} aliphatic optionally bears one or two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, -S(O₂)-, and -N(R⁵)-, and wherein said Het, fused Het, aryl or C_{1-6} aliphatic are optionally substituted by one to three of R⁵, and where Het, fused Het, R⁵ and R⁷ are as defined below;

R^3 is H, Het, fused Het, aryl, C_{1-6} aliphatic, CN, NO₂, halogen, -OR⁵, -SR⁵, -S(O)R⁵, -NR⁵R⁷, -NR⁵COR⁵, -NR⁵CO₂R⁵, -NR⁵CONR⁵R⁷, -NR⁵SO₂R⁵, -NR⁵C(NR⁵)NHR⁵, -COR⁵, -CO₂R⁵, -CONR⁵R⁷, -SO₂NR⁵R⁷, aryl-SO₂NR⁵R⁷, -OCONR⁵R⁷, or -C(NR⁵)NR⁵R⁷, where said C_{1-6} aliphatic optionally bears one to two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, -S(O₂)-, and -N(R⁵)-, where said Het, aryl or C_{1-6} aliphatic are optionally substituted by one to three of R⁵, and where Het, fused Het, R⁵ and R⁷ are as defined below;

R^4 is H, Het, fused Het, aryl, C_{1-6} aliphatic, -CN, -NO₂, halogen, -OR⁵, -SR⁵, -S(O)R⁵, -NR⁵R⁷, -NR⁵COR⁵, -NR⁵CO₂R⁵, -NR⁵CONR⁵R⁷, -NR⁵SO₂R⁵, -NR⁵C(NR⁵)NHR⁵, -COR⁵, -CO₂R⁵, -CONR⁵R⁷, -SO₂NR⁵R⁷, -OCONR⁵R⁷, or -C(NR⁵)NR⁵R⁷, where said C_{1-6} aliphatic optionally bears one or two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, -S(O₂)-, and -N(R⁵)-, and wherein said Het, fused Het, aryl or C_{1-6} aliphatic are optionally substituted by one to three of R⁵, and where Het, fused Het, R⁵ and R⁷ are as defined below;

R⁵ is H, Het, aryl, halogen, or C_{1-6} aliphatic, where said C_{1-6} aliphatic optionally bears one to two aliphatic chain insertions selected from the group consisting of

-O-, -S-, -S(O)-, -S(O₂)-, and -N(R⁶)-, where said C₁₋₆ aliphatic, aryl, or Het is optionally substituted by one to four of halogen, another Het or substituted Het, aryl or substituted aryl, -CN, -NO₂, -R⁶, -SR⁶, -OR⁶, -N(R⁶)₂, -S(O)R⁶, -SO₂R⁶, -SO₂N(R⁶)₂, NR⁶COR⁶, -NR⁶CON(R⁶)₂, -NR⁶(NR⁶)NHR⁶, -CO₂R⁶, -CON(R⁶)₂, -NR⁶SO₂R⁶, -OCON(R⁶)₂, or -NR⁶CO₂R⁶, where substituted Het and substituted aryl bear substituents that are any of -CN, -NO₂, -R⁶, -SR⁶, -OR⁶, -N(R⁶)₂, -S(O)R⁶, -SO₂R⁶, -SO₂N(R⁶)₂, NR⁶COR⁶, -NR⁶CON(R⁶)₂, -NR⁶(NR⁶)NHR⁶, -CO₂R⁶, -CON(R⁶)₂, -NR⁶SO₂R⁶, -OCON(R⁶)₂, or -NR⁶CO₂R⁶ and where Het and R⁶ are as defined below;

R⁶ is H, C₁₋₆ aliphatic, Het or aryl, where said C₁₋₁₂ aliphatic, Het or aryl is optionally substituted by one to three of halogen or OH, and where Het is as defined below;

R⁷ is H or R⁵;

Het is a five to ten membered saturated or unsaturated heterocyclic ring selected from the group consisting of acridine, benzimidazole, benzofuran, benzothiophene, benzoxazole, benzthiazole, carbazole, cinnoline, dioxin, dioxane, dioxalane, dithiane, dithiazine, dithiazole, dithiolane, furan, imidazole, imidazoline, imidazolidine, indole, indoline, indolizine, indazole, isoindole, isoquinoline, isoxazole, isothiazole, morpholine, naphthyridine, oxazole, oxadiazole, oxathiazole, oxathiazolidine, oxazine, oxadiazine, phenazine, phenothiazine, phenoxazine, phthalazine, piperazine, piperidine, pteridine, purine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrroline, quinoline, quinoxaline, quinazoline, quinolizine, tetrahydrofuran, tetrazine, tetrazole, thiophene, thiadiazine, thiadiazole, thiatriazole, thiazine, thiazole, thiomorpholine, thianaphthalene, thiopyran, triazine, triazole, and trithiane;

fused Het is where R² and R³ or where R³ and R⁴ are optionally joined to form a fused ring selected from the group consisting of 5-10 membered aryl rings, 5-10

5 membered saturated heteroaryl rings or 5-10 membered unsaturated heterocyclyl rings, said heteroaryl or said heterocyclyl rings having one to three heteratoms where zero to three of said heteratoms are N and zero to one of said heteratoms are O or S and where said fused ring is optionally substituted by one to three of R^5 , where R^5 is defined above;

10 and the pharmaceutically acceptable salts, biohydrolyzable esters, biohydrolyzable amides, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, solvates, hydrates, affinity reagents or prodrugs of (I) as defined above.

3. A compound of formula (I) as claimed in claim 1 wherein:

15 R^1 is Het or aryl, with said Het or aryl optionally substituted by one to four substituents selected from the group consisting of C_{1-6} lower alkyl, halogen, $-(CH_2)_{1-6} OH$, $-O(CH_2)_3N(CH_3)_2$, $-NO_2$, $-OR^5$, $-NH(CO)CH_3$, $-C(O)R^5$, aryloxy, $-C_6H_5SO_2NH_2$, or $-C(O)OR^5$, where Het and R^5 are as defined below;

20 R^2 is H;

R^3 is Het, $Het-R^5$, aryl, C_{1-12} aliphatic, $-COR^5$, $-CO_2R^5$, or halogen, and where Het and R^5 are as defined below;

25 R^4 is H;

R^5 is H, C_{1-12} aliphatic, $-SO_2R^6$, or $-N(R^6)_2$, where said C_{1-12} aliphatic is optionally substituted by one to four of halogen, where R^6 is as defined below;

30 R^6 is H, or NH_2 ;

Het is a five to ten membered saturated or unsaturated heterocyclic ring selected from the group consisting of pyridine, pyrrole, furan, quinoline, thiophene and thiazole,

and the pharmaceutically acceptable salts, biohydrolyzable esters, biohydrolyzable amides, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, solvates, hydrates, affinity reagents or prodrugs of (I) as defined above.

4. A compound of formula (I) as claimed in claim 1 wherein:

R^1 is substituted phenyl, Het, or substituted Het, where said phenyl substituent is independently one or more of halogen, C_{1-6} lower alkyl, $-OH$, C_{1-6} lower alkyl- OH , C_{1-6} alkoxy, $-O-C_6H_5$, C_{1-6} alkoxy substituted by amine, or amide substituted by C_{1-6} lower alkyl, and where said Het substituent is independently one or more of $-CH_3$, or $-C_6H_5-SO_2NH_2$;

R^2 is H, Het, fused Het, aryl, C_{1-12} aliphatic, $-CN$, $-NO_2$, halogen, $-OR^5$, $-SR^5$, $-S(O)R^5$, $-NR^5R^7$, $-NR^5COR^5$, $-NR^5CO_2R^5$, $-NR^5CONR^5R^7$, $-NR^5SO_2R^5$, $-NR^5C(NR^5)NHR^5$, $-COR^5$, $-CO_2R^5$, $-CONR^5R^7$, $-SO_2NR^5R^7$, $-OCONR^5R^7$, or $-C(NR^5)NR^5R^7$, where said C_{1-12} aliphatic optionally bears one or two aliphatic chain insertions selected from the group consisting of $-C(O)-$, $-O-$, $-S-$, $-S(O)-$, $-S(O_2)-$, and $-N(R^5)-$, and wherein said Het, fused Het, aryl or C_{1-12} aliphatic are optionally substituted by one to three of R^5 , and where Het, fused Het, R^5 and R^7 are as defined below;

R^3 is H, Het, fused Het, aryl, C_{1-12} aliphatic, CN , NO_2 , halogen, $-OR^5$, $-SR^5$, $-S(O)R^5$, $-NR^5R^7$, $-NR^5COR^5$, $-NR^5CO_2R^5$, $-NR^5CONR^5R^7$, $-NR^5SO_2R^5$, $-NR^5C(NR^5)NHR^5$, $-COR^5$, $-CO_2R^5$, $-CONR^5R^7$, $-SO_2NR^5R^7$, aryl- $SO_2NR^5R^7$, $-OCONR^5R^7$, or $-C(NR^5)NR^5R^7$, where said C_{1-12} aliphatic optionally bears one to two aliphatic chain insertions selected from the group consisting of $-C(O)-$, $-O-$,

-S-, -S(O)-, -S(O₂)-, and -N(R⁵)-, where said Het, aryl or C₁₋₁₂ aliphatic are optionally substituted by one to three of R⁵, and where Het, fused Het, R⁵ and R⁷ are as defined below;

5 R⁴ is H, Het, fused Het, aryl, C₁₋₁₂ aliphatic, -CN, -NO₂, halogen, -OR⁵, -SR⁵,
 -S(O)R⁵, -NR⁵R⁷, -NR⁵COR⁵, -NR⁵CO₂R⁵, -NR⁵CONR⁵R⁷, -NR⁵SO₂R⁵,
 -NR⁵C(NR⁵)NHR⁵, -COR⁵, -CO₂R⁵, -CONR⁵R⁷, -SO₂NR⁵R⁷, -OCONR⁵R⁷, or
 -C(NR⁵)NR⁵R⁷, where said C₁₋₁₂ aliphatic optionally bears one or two aliphatic
 10 chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-,
 -S(O₂)-, and -N(R⁵)-, and wherein said Het, fused Het, aryl or C₁₋₁₂ aliphatic are
 optionally substituted by one to three of R⁵, and where Het, fused Het, R⁵ and R⁷
 are as defined below;

15 R⁵ is H, Het, aryl, halogen, or C₁₋₁₂ aliphatic, where said C₁₋₁₂ aliphatic optionally
 bears one to two aliphatic chain insertions selected from the group consisting of
 -O-, -S-, -S(O)-, -S(O₂)-, and -N(R⁶)-, where said C₁₋₁₂ aliphatic, aryl, or Het is
 optionally substituted by one to four of halogen, another Het or substituted Het,
 aryl or substituted aryl, -CN, -NO₂, -R⁶, -SR⁶, -OR⁶, -N(R⁶)₂, -S(O)R⁶, -SO₂R⁶,
 -SO₂N(R⁶)₂, NR⁶COR⁶, -NR⁶CON(R⁶)₂, -NR⁶(NR⁶)NHR⁶, -CO₂R⁶, -CON(R⁶)₂,
 20 -NR⁶SO₂R⁶, -OCON(R⁶)₂, or -NR⁶CO₂R⁶, where substituted Het and substituted
 aryl are any of -CN, -NO₂, -R⁶, -SR⁶, -OR⁶, -N(R⁶)₂, -S(O)R⁶, -SO₂R⁶,
 -SO₂N(R⁶)₂, NR⁶COR⁶, -NR⁶CON(R⁶)₂, -NR⁶(NR⁶)NHR⁶, -CO₂R⁶, -CON(R⁶)₂,
 -NR⁶SO₂R⁶, -OCON(R⁶)₂, or -NR⁶CO₂R⁶ and where Het and R⁶ are as defined
 below;

25 R⁶ is H, C₁₋₁₂ aliphatic, Het or aryl, where said C₁₋₁₂ aliphatic, Het or aryl is
 optionally substituted by one to three of halogen or OH, and where Het is as
 defined below;

30 R⁷ is H or R⁵;

Het is a five to ten membered saturated or unsaturated heterocyclic ring selected from the group consisting of acridine, benzimidazole, benzofuran, benzothiophene, benzoxazole, benzthiazole, carbazole, cinnoline, dioxin, dioxane, dioxalane, dithiane, dithiazine, dithiazole, dithiolane, furan, imidazole, imidazoline, imidazolidine, indole, indoline, indolizine, indazole, isoindole, isoquinoline, isoxazole, isothiazole, morpholine, naphthyridine, oxazole, oxadiazole, oxathiazole, oxathiazolidine, oxazine, oxadiazine, phenazine, phenothiazine, phenoxazine, phthalazine, piperazine, piperidine, pteridine, purine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrroline, quinoline, quinoxaline, quinazoline, quinolizine, tetrahydrofuran, tetrazine, tetrazole, thiophene, thiadiazine, thiadiazole, thiatriazole, thiazine, thiazole, thiomorpholine, thianaphthalene, thiopyran, triazine, triazole, and trithiane;

fused Het is where R^2 and R^3 or where R^3 and R^4 are optionally joined to form a fused ring selected from the group consisting of 5-10 membered aryl rings, 5-10 membered saturated heteroaryl rings or 5-10 membered unsaturated heterocyclyl rings, said heteroaryl or said heterocyclyl rings having one to three heteroatoms where zero to three of said heteroatoms are N and zero to one of said heteroatoms are O or S and where said fused ring is optionally substituted by one to three of R^5 , where R^5 is defined above;

and the pharmaceutically acceptable salts, biohydrolyzable esters, biohydrolyzable amides, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, solvates, hydrates, affinity reagents or prodrugs of (I) as defined above.

5. A compound of formula (I) as claimed in claim 4 wherein:

R^1 is substituted phenyl, Het, or substituted Het, where said phenyl substituent is independently one or more of halogen, C_{1-6} lower alkyl, -OH, C_{1-6} lower alkyl-OH,

C₁₋₆ alkoxy, -O-C₆H₅, C₁₋₆ alkoxy substituted by amine, or amide substituted by C₁₋₆ lower alkyl, and where said Het substituent is independently one or more of -CH₃, or -C₆H₅-SO₂NH₂ ;

5

R² is H, Het, fused Het, aryl, C₁₋₆ aliphatic, -CN, -NO₂, halogen, -OR⁵, -SR⁵, -S(O)R⁵, -NR⁵R⁷, -NR⁵COR⁵, -NR⁵CO₂R⁵, -NR⁵CONR⁵R⁷, -NR⁵SO₂R⁵, -NR⁵C(NR⁵)NHR⁵, -COR⁵, -CO₂R⁵, -CONR⁵R⁷, -SO₂NR⁵R⁷, -OCONR⁵R⁷, or -C(NR⁵)NR⁵R⁷, where said C₁₋₆ aliphatic optionally bears one or two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, -S(O₂)-, and -N(R⁵)-, and wherein said Het, fused Het, aryl or C₁₋₆ aliphatic are optionally substituted by one to three of R⁵, and where Het, fused Het, R⁵ and R⁷ are as defined below;

10

15

20

R³ is H, Het, fused Het, aryl, C₁₋₆ aliphatic, CN, NO₂, halogen, -OR⁵, -SR⁵, -S(O)R⁵, -NR⁵R⁷, -NR⁵COR⁵, -NR⁵CO₂R⁵, -NR⁵CONR⁵R⁷, -NR⁵SO₂R⁵, -NR⁵C(NR⁵)NHR⁵, -COR⁵, -CO₂R⁵, -CONR⁵R⁷, -SO₂NR⁵R⁷, aryl-SO₂NR⁵R⁷, -OCONR⁵R⁷, or -C(NR⁵)NR⁵R⁷, where said C₁₋₆ aliphatic optionally bears one to two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, -S(O₂)-, and -N(R⁵)-, where said Het, aryl or C₁₋₆ aliphatic are optionally substituted by one to three of R⁵, and where Het, fused Het, R⁵ and R⁷ are as defined below;

25

30

R⁴ is H, Het, fused Het, aryl, C₁₋₆ aliphatic, -CN, -NO₂, halogen, -OR⁵, -SR⁵, -S(O)R⁵, -NR⁵R⁷, -NR⁵COR⁵, -NR⁵CO₂R⁵, -NR⁵CONR⁵R⁷, -NR⁵SO₂R⁵, -NR⁵C(NR⁵)NHR⁵, -COR⁵, -CO₂R⁵, -CONR⁵R⁷, -SO₂NR⁵R⁷, -OCONR⁵R⁷, or -C(NR⁵)NR⁵R⁷, where said C₁₋₆ aliphatic optionally bears one or two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, -S(O₂)-, and -N(R⁵)-, and wherein said Het, fused Het, aryl or C₁₋₆ aliphatic are optionally substituted by one to three of R⁵, and where Het, fused Het, R⁵ and R⁷ are as defined below;

R^5 is H, Het, aryl, halogen, or C_{1-6} aliphatic, where said C_{1-6} aliphatic optionally bears one to two aliphatic chain insertions selected from the group consisting of -O-, -S-, -S(O)-, -S(O₂)-, and -N(R⁶)-, where said C_{1-6} aliphatic, aryl, or Het is optionally substituted by one to four of halogen, another Het or substituted Het, aryl or substituted aryl, -CN, -NO₂, -R⁶, -SR⁶, -OR⁶, -N(R⁶)₂, -S(O)R⁶, -SO₂R⁶, -SO₂N(R⁶)₂, NR⁶COR⁶, -NR⁶CON(R⁶)₂, -NR⁶(NR⁶)NHR⁶, -CO₂R⁶, -CON(R⁶)₂, -NR⁶SO₂R⁶, -OCON(R⁶)₂, or -NR⁶CO₂R⁶, where substituted Het and substituted aryl are any of -CN, -NO₂, -R⁶, -SR⁶, -OR⁶, -N(R⁶)₂, -S(O)R⁶, -SO₂R⁶, -SO₂N(R⁶)₂, NR⁶COR⁶, -NR⁶CON(R⁶)₂, -NR⁶(NR⁶)NHR⁶, -CO₂R⁶, -CON(R⁶)₂, -NR⁶SO₂R⁶, -OCON(R⁶)₂, or -NR⁶CO₂R⁶ and where Het and R⁶ are as defined below;

R^6 is H, C_{1-6} aliphatic, Het or aryl, where said C_{1-12} aliphatic, Het or aryl is optionally substituted by one to three of halogen or OH, and where Het is as defined below;

R^7 is H or R⁵;

Het is a five to ten membered saturated or unsaturated heterocyclic ring selected from the group consisting of acridine, benzimidazole, benzofuran, benzothiophene, benzoxazole, benzthiazole, carbazole, cinnoline, dioxin, dioxane, dioxalane, dithiane, dithiazine, dithiazole, dithiolane, furan, imidazole, imidazoline, imidazolidine, indole, indoline, indolizine, indazole, isoindole, isoquinoline, isoxazole, isothiazole, morpholine, naphthyridine, oxazole, oxadiazole, oxathiazole, oxathiazolidine, oxazine, oxadiazine, phenazine, phenothiazine, phenoxazine, phthalazine, piperazine, piperidine, pteridine, purine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrroline, quinoline, quinoxaline, quinazoline, quinolizine, tetrahydrofuran, tetrazine, tetrazole, thiophene, thiadiazine, thiadiazole, thiatriazole, thiazine, thiazole, thiomorpholine, thianaphthalene, thiopyran, triazine, triazole, and trithiane;

fused Het is where R^2 and R^3 or where R^3 and R^4 are optionally joined to form a fused ring selected from the group consisting of 5-10 membered aryl rings, 5-10 membered saturated heteroaryl rings or 5-10 membered unsaturated heterocyclyl rings, said heteroaryl or said heterocyclyl rings having one to three heteratoms where zero to three of said heteratoms are N and zero to one of said heteratoms are O or S and where said fused ring is optionally substituted by one to three of R^5 , where R^5 is defined above;

and the pharmaceutically acceptable salts, biohydrolyzable esters, biohydrolyzable amides, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, solvates, hydrates, affinity reagents or prodrugs of (I) as defined above.

6. A compound of formula (I) as claimed in claim 4 wherein:

R^1 is substituted phenyl, Het, or substituted Het, where said phenyl substituent is independently one or more of halogen, C_{1-6} lower alkyl, -OH, C_{1-6} lower alkyl-OH, C_{1-6} alkoxy, -O- C_6H_5 , C_{1-6} alkoxy substituted by amine, or amide substituted by C_{1-6} lower alkyl, and where said Het substituent is independently one or more of -CH₃, or - C_6H_5 -SO₂NH₂ ;

R^2 is H;

R^3 is Het, Het- R^5 , aryl, C_{1-12} aliphatic, -COR⁵, -CO₂R⁵, or halogen, and where Het and R^5 are as defined below;

R^4 is H;

R^5 is H, C_{1-12} aliphatic, -SO₂R⁶, or -N(R^6)₂, where said C_{1-12} aliphatic is optionally substituted by one to four of halogen, where R^6 is as defined below;

R^6 is H, or NH₂;

Het is a five to ten membered saturated or unsaturated heterocyclic ring selected from the group consisting of pyridine, pyrrole, furan, quinoline, thiophene and thiazole,

and the pharmaceutically acceptable salts, biohydrolyzable esters, biohydrolyzable amides, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, solvates, hydrates, affinity reagents or prodrugs of (I) as defined above.

7. A compound of formula (I) as claimed in claim 4 wherein:

R^1 is phenyl, substituted phenyl, Het, or substituted Het, where said phenyl substituent is independently one or more of Br, F, -OH, -CH₂OH, -O-CH₃, -O-C₆H₅, -O-(CH₂)₃NH₂, -C(CH₃)₂, or -NHCOCH₃, and where said Het substituent is independently one or more of -CH₃, or -C₆H₅-SO₂NH₂.

R^2 is H, Het, fused Het, aryl, C₁₋₁₂ aliphatic, -CN, -NO₂, halogen, -OR⁵, -SR⁵, -S(O)R⁵, -NR⁵R⁷, -NR⁵COR⁵, -NR⁵CO₂R⁵, -NR⁵CONR⁵R⁷, -NR⁵SO₂R⁵, -NR⁵C(NR⁵)NHR⁵, -COR⁵, -CO₂R⁵, -CONR⁵R⁷, -SO₂NR⁵R⁷, -OCONR⁵R⁷, or -C(NR⁵)NR⁵R⁷, where said C₁₋₁₂ aliphatic optionally bears one or two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-, -S(O₂)-, and -N(R⁵)-, and wherein said Het, fused Het, aryl or C₁₋₁₂ aliphatic are optionally substituted by one to three of R⁵, and where Het, fused Het, R⁵ and R⁷ are as defined below;

R^3 is H, Het, fused Het, aryl, C₁₋₁₂ aliphatic, CN, NO₂, halogen, -OR⁵, -SR⁵, -S(O)R⁵, -NR⁵R⁷, -NR⁵COR⁵, -NR⁵CO₂R⁵, -NR⁵CONR⁵R⁷, -NR⁵SO₂R⁵, -NR⁵C(NR⁵)NHR⁵, -COR⁵, -CO₂R⁵, -CONR⁵R⁷, -SO₂NR⁵R⁷, aryl-SO₂NR⁵R⁷, -OCONR⁵R⁷, or -C(NR⁵)NR⁵R⁷, where said C₁₋₁₂ aliphatic optionally bears one to two aliphatic chain insertions selected from the group consisting of -C(O)-, -O-,

-S-, -S(O)-, -S(O₂)-, and -N(R⁵)-, where said Het, aryl or C₁₋₁₂ aliphatic are optionally substituted by one to three of R⁵, and where Het, fused Het, R⁵ and R⁷ are as defined below;

5 R⁴ is H, Het, fused Het, aryl, C₁₋₁₂ aliphatic, -CN, -NO₂, halogen, -OR⁵, -SR⁵,
 -S(O)R⁵, -NR⁵R⁷, -NR⁵COR⁵, -NR⁵CO₂R⁵, -NR⁵CONR⁵R⁷, -NR⁵SO₂R⁵,
 -NR⁵C(NR⁵)NHR⁵, -COR⁵, -CO₂R⁵, -CONR⁵R⁷, -SO₂NR⁵R⁷, -OCONR⁵R⁷, or
 -C(NR⁵)NR⁵R⁷, where said C₁₋₁₂ aliphatic optionally bears one or two aliphatic
 10 chain insertions selected from the group consisting of -C(O)-, -O-, -S-, -S(O)-,
 -S(O₂)-, and -N(R⁵)-, and wherein said Het, fused Het, aryl or C₁₋₁₂ aliphatic are
 optionally substituted by one to three of R⁵, and where Het, fused Het, R⁵ and R⁷
 are as defined below;

15 R⁵ is H, Het, aryl, halogen, or C₁₋₁₂ aliphatic, where said C₁₋₁₂ aliphatic optionally
 bears one to two aliphatic chain insertions selected from the group consisting of
 -O-, -S-, -S(O)-, -S(O₂)-, and -N(R⁶)-, where said C₁₋₁₂ aliphatic, aryl, or Het is
 optionally substituted by one to four of halogen, another Het or substituted Het,
 aryl or substituted aryl, -CN, -NO₂, -R⁶, -SR⁶, -OR⁶, -N(R⁶)₂, -S(O)R⁶, -SO₂R⁶,
 -SO₂N(R⁶)₂, NR⁶COR⁶, -NR⁶CON(R⁶)₂, -NR⁶(NR⁶)NHR⁶, -CO₂R⁶, -CON(R⁶)₂,
 20 -NR⁶SO₂R⁶, -OCON(R⁶)₂, or -NR⁶CO₂R⁶, where substituted Het and substituted
 aryl are any of -CN, -NO₂, -R⁶, -SR⁶, -OR⁶, -N(R⁶)₂, -S(O)R⁶, -SO₂R⁶,
 -SO₂N(R⁶)₂, NR⁶COR⁶, -NR⁶CON(R⁶)₂, -NR⁶(NR⁶)NHR⁶, -CO₂R⁶, -CON(R⁶)₂,
 -NR⁶SO₂R⁶, -OCON(R⁶)₂, or -NR⁶CO₂R⁶ and where Het and R⁶ are as defined
 below;

25 R⁶ is H, C₁₋₁₂ aliphatic, Het or aryl, where said C₁₋₁₂ aliphatic, Het or aryl is
 optionally substituted by one to three of halogen or OH, and where Het is as
 defined below;

30 R⁷ is H or R⁵;

Het is a five to ten membered saturated or unsaturated heterocyclic ring selected from the group consisting of pyrrole, furan, thiophene, pyrazole, or indole.

5 fused Het is where R^2 and R^3 or where R^3 and R^4 are optionally joined to form a fused ring selected from the group consisting of 5-10 membered aryl rings, 5-10 membered saturated heteroaryl rings or 5-10 membered unsaturated heterocyclyl rings, said heteroaryl or said heterocyclyl rings having one to three heteratoms where zero to three of said heteratoms are N and zero to one of said heteratoms are O or S and where said fused ring is optionally substituted by one
10 to three of R^5 , where R^5 is defined above;

and the pharmaceutically acceptable salts, biohydrolyzable esters, biohydrolyzable amides, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, solvates, hydrates, affinity reagents or
15 prodrugs of (I) as defined above.

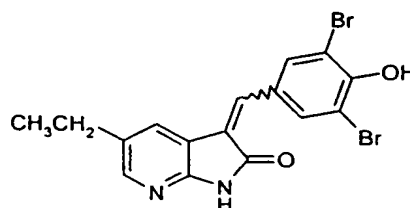
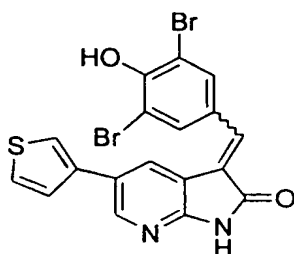
8. A compound as claimed in any one of claims 1 to 7, wherein R^1 is phenyl substituted at the para- position by -OH and said -OH is conjugated with a carbamoyl conjugate to yield a biohydrolyzable carbamate wherein said
20 carbamoyl conjugate is selected from the group consisting of diethylaminocarbonyl, N-(2-hydroxyethyl)aminocarbonyl, N,N,-bis(2-hydroxyethyl)aminocarbonyl, hydroxyethyloxyethylaminocarbonyl, 4-morpholinocarbonyl and 4-methyl-1-piperazinylcarbonyl.

9. A compound as claimed in any one of claims 1 to 7, wherein R^1 is phenyl substituted at the para-position by -OH and said -OH is conjugated with a carbonate conjugate to yield a biohydrolyzable carbonate wherein said carbonyl
25 conjugate is selected from the group consisting of phenylmethyloxyxcarbonyl, ethyloxyxcarbonyl, isobutyloxyxcarbonyl, and pyridinemethyloxyxcarbonyl.

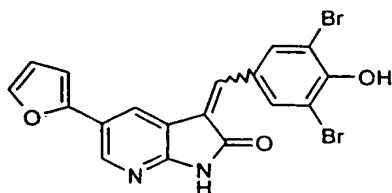
30 10. A compound as claimed in any one of claims 1 to 7, wherein R^1 is phenyl substituted at the para-position by -OH and said OH is conjugated with an ester

conjugate to yield a biohydrolyzable ester wherein said ester conjugate is selected from the group consisting of t-butylcarbonyloxymethyl.

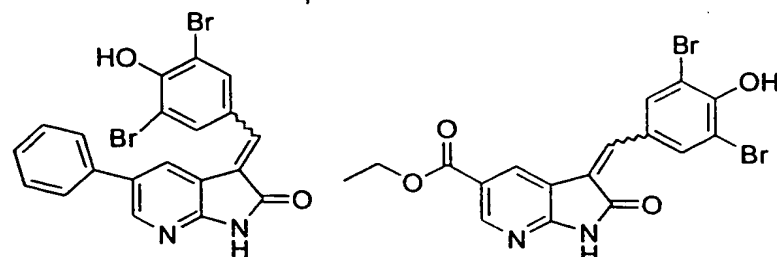
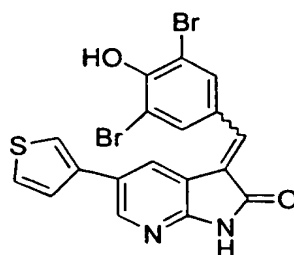
11. A compound as claimed in claim 1, selected from the group consisting of



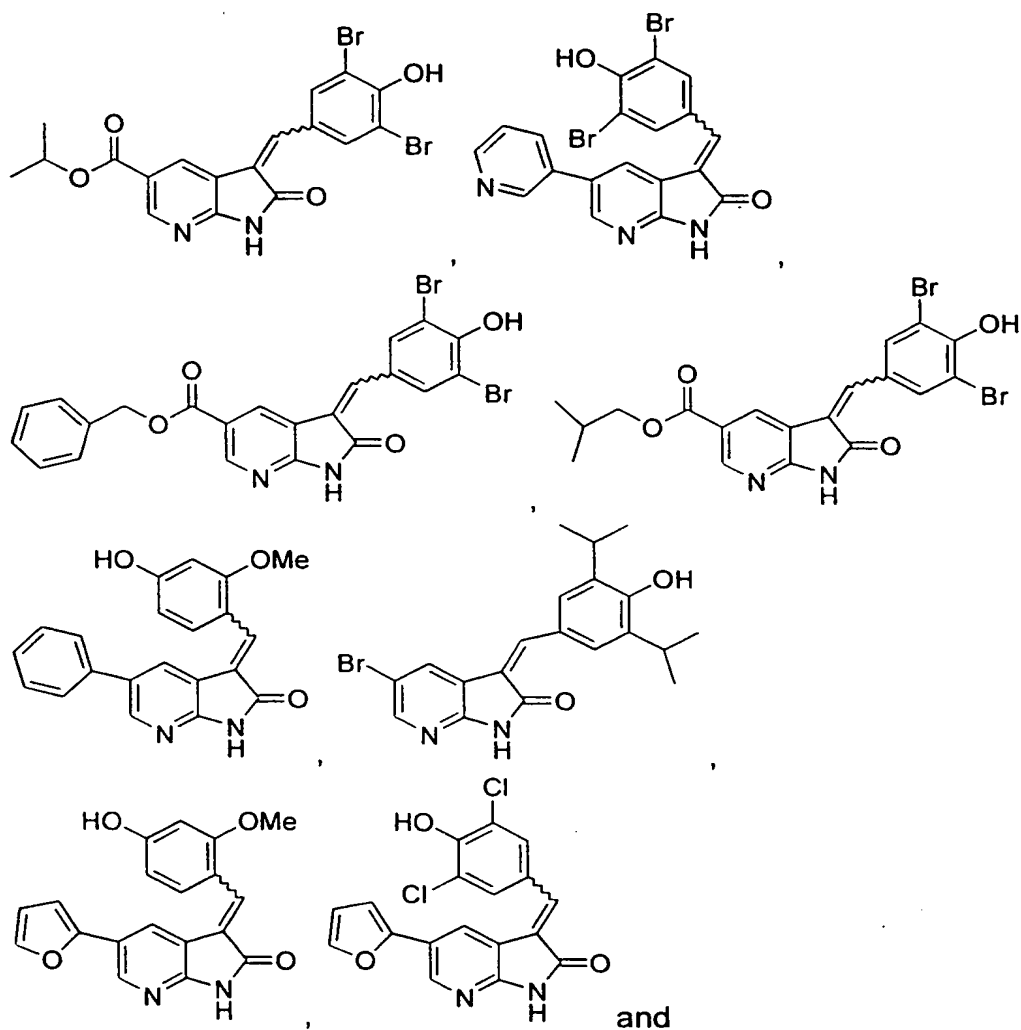
and



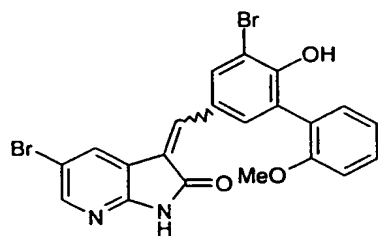
12. A compound as claimed in claim 1, selected from the group consisting of



125



5



13. The compound 3-(3,5-Dibromo-4-hydroxy-benzylidene)-5-phenyl-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one

14. The compound 3-(3,5-Dibromo-4-hydroxy-benzylidene)-5-furan-2-yl-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one

5 15. The compound 3-(3,5-Dibromo-4-hydroxy-benzylidene)-5-thiophen-3-yl-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one

16. A compound as claimed in any one of claims 1 to 15, wherein said compound is in the E geometric isomer form.

10 17. A compound as claimed in any one of claims 1 to 15, wherein said compound is in the Z geometric isomer form.

15 18. A compound as claimed in any one of claims 1 to 15, wherein said compound is a mixture of the Z geometric isomer form and the E geometric isomer form.

19. A compound as claimed in any one of claims 1 to 15, having a chiral carbon atom and which compound is dextrorotatory.

20 20. A compound as claimed in any one of claims 1 to 15, having a chiral carbon atom and which compound is levorotatory.

25 21. A compound as claimed in any one of claims 1 to 15, having a chiral carbon atom and which is a mixture of dextrorotatory and levorotatory.

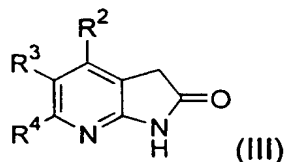
22. A compound as claimed in any one of claims 1 to 21 for use in therapy.

30 23. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a pharmacologically effective amount of a compound as claimed in any one of claims 1 to 21.

24. A process for the preparation of a compound of formula (I) as claimed in claim 1, which comprises the reaction of a compound of formula (II)

R^1CHO (II)

wherein R^1 is as defined in claim 1, with a compound of formula (III)



wherein R^2 , R^3 and R^4 are as defined in claim 1.

25. The use of a compound as claimed in any one of claims 1 to 21 in the preparation of a medicament for the treatment of a disease mediated by a mitogen activated protein kinase.

26. The use of a compound as claimed in any one of claims 1 to 21 in the preparation of a medicament for the treatment of a disease mediated by a kinase selected from the group consisting of ab1, ATK, bcr-ab1, Blk, Brk, Btk, c-kit, c-met, c-src, CDK1, CDK2, CDK4, CDK6, cRaf1, CSF1R, CSK, EGFR, ErbB2, ErbB3, ErbB4, ERK, Fak, fes, FGFR1, FGFR2, FGFR3, FGFR4, FGFR5, Fgr, FLK-4, flt-1, Fps, Frk, Fyn, GSK, Hck, IGF-1R, INS-R, Jak, JNK, KDR, Lck, Lyn, MEK, p38, PDGFR, PIK, PKC, PYK2, ros, tie₁, tie₂, TRK, UL97, Yes and Zap70.

27. The use of a compound as claimed in any one of claims 1 to 21 in the preparation of a medicament for the treatment of a disease mediated by cRaf1 kinase.

28. The use of a compound as claimed in any one of claims 1 to 21 in the preparation of a medicament for the treatment of a disease mediated by p38 kinase.

29. The use of a compound as claimed in any one of claims 1 to 21 in the preparation of a medicament for the treatment of a disease mediated by VEGFR kinase.

5 30. The use of a compound as claimed in any one of claims 1 to 21 in the preparation of a medicament for the treatment of a disease mediated by Tie2 kinase.

10 31. The use of a compound as claimed in any one of claims 1 to 21 in the preparation of a medicament for the treatment of a disease mediated by c-fms kinase.

15 32. The use of a compound as claimed in any one of claims 1 to 21 in the preparation of a medicament for inhibiting tumor growth, preventing organ transplant rejection, healing a chronic wound, or for treating a disease state selected from the group consisting of restenosis, rheumatoid arthritis, angiogenesis, hepatic cirrhosis, atherosclerosis, glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, glomerulopathy, psoriasis, asthma, diabetes mellitus, inflammation, and
20 neurodegenerative disease.

25 33. A method of treating a disease mediated by a mitogen activated protein kinase, comprising the step of administering to a mammal in need thereof a pharmacologically effective amount of a compound as claimed in any one of claims 1 to 21.

30 34. A method of treating a disease mediated by a kinase selected from the group consisting of ab1, ATK, bcr-ab1, Blk, Brk, Btk, c-kit, c-met, c-src, CDK1, CDK2, CDK4, CDK6, cRaf1, CSF1R, CSK, EGFR, ErbB2, ErbB3, ErbB4, ERK, Fak, fes, FGFR1, FGFR2, FGFR3, FGFR4, FGFR5, Fgr, FLK-4, flt-1, Fps, Frk, Fyn, GSK, Hck, IGF-1R, INS-R, Jak, JNK, KDR, Lck, Lyn, MEK, p38, PDGFR, PIK, PKC, PYK2, ros, tie₁, tie₂, TRK, UL97, Yes and Zap70, said method

comprising the step of administering to a mammal in need thereof a pharmacologically effective amount of a compound as claimed in any one of claims 1 to 21.

- 5 35. A method of treating a disease mediated by cRaf1 kinase, said method comprising the step of administering to a mammal in need thereof a pharmacologically effective amount of a compound as claimed in any one of claims 1 to 21.
- 10 36. A method of treating a disease mediated by p38 kinase, said method comprising the step of administering to a mammal in need thereof a pharmacologically effective amount of a compound as claimed in any one of claims 1 to 21.
- 15 37. A method of treating a disease mediated by VEGFR kinase, said method comprising the step of administering to a mammal in need thereof a pharmacologically effective amount of a compound as claimed in any one of claims 1 to 21.
- 20 38. A method of treating a disease mediated by Tie2 kinase, said method comprising the step of administering to a mammal in need thereof a pharmacologically effective amount of a compound as claimed in any one of claims 1 to 21.
- 25 39. A method of treating a disease mediated by c-fms kinase, said method comprising the step of administering to a mammal in need thereof a pharmacologically effective amount of a compound as claimed in any one of claims 1 to 21.
- 30 40. A method of inhibiting tumor growth, preventing organ transplant rejection, healing a chronic wound, or of treating a disease state selected from the group consisting of restenosis, rheumatoid arthritis, angiogenesis, hepatic cirrhosis,

- 5 atherosclerosis, glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, glomerulopathy, psoriasis, asthma, diabetes mellitus, inflammation, and neurodegenerative disease, comprising the step of administering to a patient in need thereof a pharmacologically effective amount of a compound as claimed in any one of claims 1 to 21.

INTERNATIONAL SEARCH REPORT

In International Application No

PC 98/06357

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D471/04 A61K31/435 //(C07D471/04,221:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 16964 A (PHARMACIA) 6 June 1996 see claims 1,6 -----	1,23

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

9 March 1999

Date of mailing of the international search report

17/03/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Alfaro Faus, I

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 98/ 06357

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 33 to 40
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 33 to 40
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inventor's Application No

PCT/98/06357

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9616964 A	06-06-1996	AU 3926295 A	19-06-1996
		CA 2180730 A	06-06-1996
		CN 1139929 A	08-01-1997
		EP 0741726 A	13-11-1996
		FI 962954 A	24-07-1996
		HU 74875 A	28-02-1997
		JP 9508924 T	09-09-1997
		NO 963066 A	23-07-1996
		NZ 295668 A	24-11-1997
		PL 315689 A	25-11-1996
		US 5719135 A	17-02-1998
		ZA 9509927 A	10-06-1996

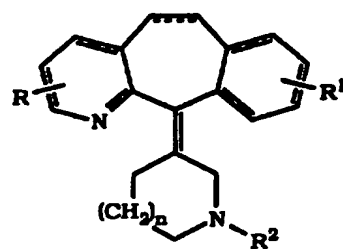




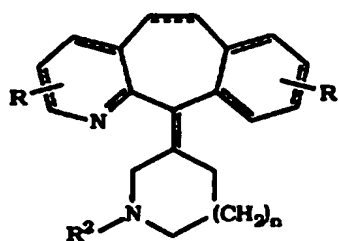
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/445, 31/44	A1	(11) International Publication Number: WO 96/30017 (43) International Publication Date: 3 October 1996 (03.10.96)
(21) International Application Number: PCT/US96/03306 (22) International Filing Date: 20 March 1996 (20.03.96) (30) Priority Data: 08/410,442 24 March 1995 (24.03.95) US (71) Applicant: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033 (US). (72) Inventors: AFONSO, Adriano; 100 Woodmere Road, West Caldwell, NJ 07006 (US). KELLY, Joseph, M.; 112 Princeton Road, Parlin, NJ 08859 (US). WOLIN, Ronald, L.; 406 Mountain Avenue, Westfield, NJ 07090 (US). (74) Agents: JEANETTE, Henry, C. et al.; Schering-Plough Corporation, Patent Dept. K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).		(81) Designated States: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>

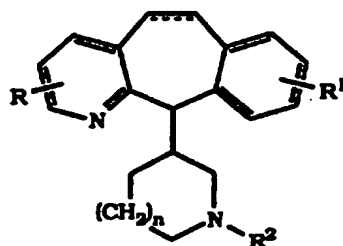
(54) Title: **TRICYCLIC COMPOUNDS USEFUL FOR INHIBITION OF G-PROTEIN FUNCTION AND FOR TREATMENT OF PROLIFERATIVE DISEASES**



(Ia)



(Ib)



(Ic)

(57) Abstract

A method of inhibiting Ras function and therefore inhibiting cellular growth is disclosed. The method comprises the administration of a novel compound of formula (Ia), (Ib) or (Ic) wherein: R and R¹ are H, alkyl, halogeno, OH, alkoxy, NH₂, alkylamino, dialkylamino, CF₃, SO₃H, CO₂R³, NO₂, SO₂NH₂, or CONHR⁴; n is 0 or 1; R² is a group of the formula R⁵C(O)-, R⁵CH₂C(O)-, R⁵C(R⁶)₂C(O)-, R⁵SO₂-, R⁵CH₂SO₂-, R⁵SCH₂C(O)-, R⁵OC(O)-, R⁵NHC(O)-, R⁵C(O)C(O)- or R⁵SC(O)-; R⁵ is alkyl, aryl, arylalkyl, arylalkenyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl or heterocycloalkyl; and R⁶ is alkyl or C(R⁶)₂ is a carboxylic ring; or pharmaceutically acceptable salts thereof.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

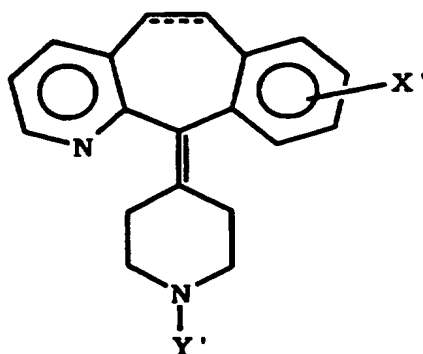
**TRICYCLIC COMPOUNDS USEFUL FOR INHIBITION OF
G-PROTEIN FUNCTION AND FOR TREATMENT OF
PROLIFERATIVE DISEASES**

5

BACKGROUND

International Publication Number WO92/11034, published July 9, 1992, discloses a method of increasing the sensitivity of a tumor to an antineoplastic agent, which tumor is resistant to the antineoplastic agent, by the concurrent administration of the antineoplastic agent and a potentiating agent of the formula:

10



wherein Y' is hydrogen, substituted carboxylate or substituted sulfonyl. Examples of such potentiating agents include 11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridines such as Loratadine.

15

To acquire transforming potential, the precursor of the Ras oncoprotein must undergo farnesylation of the cysteine residue located in a carboxyl-terminal tetrapeptide. Inhibitors of the enzyme that catalyzes this modification, farnesyl protein transferase, have therefore been suggested as anticancer agents for tumors in which Ras contributes to transformation. Mutated, oncogenic forms of ras are frequently found in many human cancers, most notably in more than 50% of colon and pancreatic carcinomas (Kohl et al., Science, Vol. 260, 1834 to 1837, 1993).

20

25

A welcome contribution to the art would be compounds useful for the inhibition of farnesyl protein transferase. Such a contribution is provided by this invention.

SUMMARY OF THE INVENTION

30

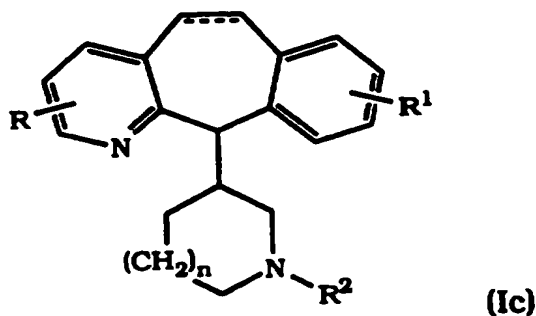
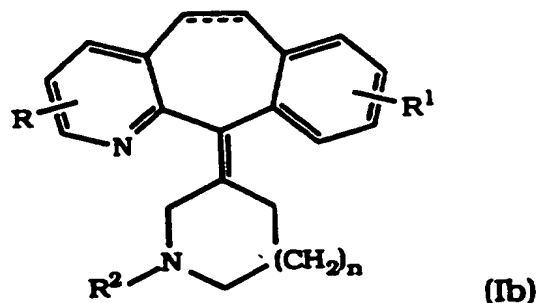
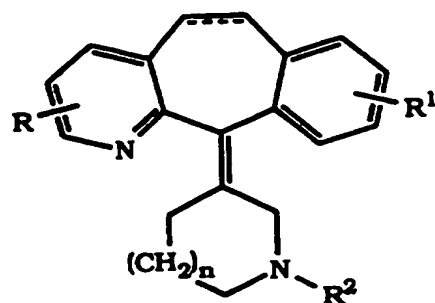
This invention provides a method for inhibiting farnesyl protein transferase (FPT) using the tricyclic compounds

- 2 -

- described below which: (i) potentially inhibit FPT, but not geranylgeranyl protein transferase I, *in vitro*; (ii) block the phenotypic change induced by a form of transforming Ras which is a farnesyl acceptor but not by a form of transforming Ras engineered to be a geranylgeranyl acceptor; (iii) block intracellular processing of Ras which is a farnesyl acceptor but not of Ras engineered to be a geranylgeranyl acceptor; and (iv) block abnormal cell growth in culture induced by transforming Ras.

This invention also provides a method for inhibiting the abnormal growth of cells, including transformed cells, by administering an effective amount of a compound of the present invention. Abnormal growth of cells means cell growth independent of normal regulatory mechanisms (e.g., loss of contact inhibition), including the abnormal growth of: (1) tumor cells (tumors) expressing an activated Ras oncogene; (2) tumor cells in which the Ras protein is activated as a result of oncogenic mutation in another gene; and (3) benign and malignant cells of other proliferative diseases in which aberrant Ras activation occurs.

This invention provides compounds of the formula (Ia), (Ib) and (Ic)



wherein:

R and R¹ are independently selected from H, (C₁-C₆)alkyl, halogeno, OH, (C₁-C₆)alkoxy; NH₂; (C₁-C₆)alkylamino; di((C₁-C₆)alkyl)amino; CF₃; SO₃H; CO₂R³; NO₂; SO₂NH₂; and CONHR⁴;

R² is R⁵C(O)-, R⁵CH₂C(O)-, R⁵C(R⁶)₂C(O)-, R⁵SO₂-,
 5 R⁵CH₂SO₂-, R⁵SCH₂C(O)-, R⁵OC(O)-, R⁵NHC(O)-, R⁵C(O)C(O)- or R⁵OC(S)-;

R³ is (C₁-C₆)alkyl, aryl;

R is (C₁-C₆)alkyl;

R⁵ is (C₁-C₆)alkyl, aryl, aryl(C₁-C₆)alkyl, aryl(C₂-C₆)alkenyl,
 10 heteroaryl, heteroaryl(C₁-C₆)alkyl, heteroaryl(C₂-C₆)alkenyl or heterocycloalkyl;

Each R⁶ independently represents (C₁-C₆)alkyl, or both R⁴ groups together with the carbon atom to which they are attached comprise a (C₃-C₇)carbocyclic ring;

15 n is 0 or 1; and

the dotted line represents an optional double bond;
 and pharmaceutically acceptable salts thereof.

This invention also provides a method for inhibiting tumor growth by administering an effective amount of the tricyclic
 20 compounds, described herein, to a mammal (e.g., a human) in need of such treatment. In particular, this invention provides a method for inhibiting the growth of tumors expressing an activated Ras oncogene by the administration of an effective amount of the above described compounds. Examples of tumors
 25 which may be inhibited include, but are not limited to, lung cancer (e.g., lung adenocarcinoma), pancreatic cancers (e.g., pancreatic carcinoma such as, for example, exocrine pancreatic carcinoma), colon cancers (e.g., colorectal carcinomas, such as, for example, colon adenocarcinoma and colon adenoma), myeloid
 30 leukemias (for example, acute myelogenous leukemia (AML)), thyroid follicular cancer, bladder carcinoma, and myelodysplastic syndrome (MDS).

It is believed that this invention also provides a method for inhibiting proliferative diseases, both benign and malignant,
 35 wherein Ras proteins are aberrantly activated as a result of oncogenic mutation in other genes--i.e., the Ras gene itself is not activated by mutation to an oncogenic form--with said inhibition being accomplished by the administration of an effective amount

of the tricyclic compounds described herein, to a mammal (e.g., a human) in need of such treatment. For example, the benign proliferative disorder neurofibromatosis, or tumors in which Ras is activated due to mutation or overexpression of tyrosine kinase oncogenes (e.g., neu, src, abl, lck, lyn, fyn), may be inhibited by
5 the tricyclic compounds described herein.

The compounds of this invention inhibit farnesyl protein transferase and the farnesylation of the oncogene protein Ras. This invention further provides a method of inhibiting ras farnesyl
10 protein transferase, in mammals, especially humans, by the administration of an effective amount of the tricyclic compounds described above. The administration of the compounds of this invention to patients, to inhibit farnesyl protein transferase, is useful in the treatment of the cancers described above.

15 The tricyclic compounds useful in the methods of this invention inhibit abnormal cellular growth. Without wishing to be bound by theory, it is believed that these compounds may function through the inhibition of G-protein function, such as ras p21, by blocking G-protein isoprenylation, thus making them useful in the
20 treatment of proliferative diseases such as tumor growth and cancer. Without wishing to be bound by theory, it is believed that these compounds inhibit ras farnesyl protein transferase, and thus show antiproliferative activity against ras transformed cells.

DETAILED DESCRIPTION OF THE INVENTION

25 As used herein, the following terms are used as defined below unless otherwise indicated:

"alkyl", including the alkyl portions of alkoxy, alkylamino and dialkylamino, means a straight or branched carbon chain containing from one to twenty carbon atoms, preferably one to six
30 carbon atoms;

"alkenyl" means an alkyl group containing one or two double bonds;

"heterocycloalkyl" means a saturated carbocyclic ring containing from 3 to 7 carbon atoms, preferably from 4 to 6
35 carbon atoms, which carbocyclic ring is interrupted by 1 to 3 heteroatoms selected from O, S and N, and includes heterocycloalkyls such as 2- or 3-tetrahydrofuranyl, 2-, 3- or 4-tetrahydropyranyl, 2- or 3- tetrahydrothienyl, 2-, 3- or 4-

piperidiny, 2- or 3-pyrrolidiny, 2- or 3-piperaziny and 2- or 3-dioxany;

5 "aryl" represents a carbocyclic aromatic group containing from 6 to 10 carbon atoms, such as phenyl or naphthyl, said carbocyclic group being optionally substituted with 1-3 substituents selected from halogeno, (C₁-C₆)alkyl, hydroxy, (C₁-C₆)alkoxy, phenoxy, CF₃, amino, alkylamino, dialkylamino, CH₃C(O)NH-, CH₃C(O)O-, NO₂ and -COOR⁸, wherein R⁸ is H or (C₁-C₆)alkyl;

10 "halogeno" means fluoro, chloro, bromo and iodo; and

"heteroaryl" means a cyclic aromatic group, containing 5 to 10 ring members, comprising 2 to 9 carbon atoms and 1 to 3 heteroatoms selected from O, S, N and N→O, wherein N→O represents an N-oxide, and includes heteroaryls such as 2-, 3- or 4-pyridyl, 2-, 3- or 4- pyridyl N-oxide, imidazolyl, pyrazolyl, triazolyl, thienyl and furanyl, which heteroaryl group is optionally substituted by 1 to 3 substituents selected from halogeno, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, amino, alkylamino, dialkylamino, C₆H₅C(O)NHCH₂- and -COOR⁸, wherein R⁸ is H or (C₁-C₆)alkyl.

20 Lines drawn into the ring systems indicate that the indicated bond may be attached to any of the substitutable ring carbon atoms.

Certain compounds of the invention may exist in different isomeric forms (e.g., enantiomers and diastereoisomers). The invention contemplates all such isomers both in pure form and in admixture, including racemic mixtures. Enol forms are also included.

30 The compounds of the invention can exist in unsolvated as well as solvated forms, including hydrated forms, e.g., hemihydrate. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol and the like are equivalent to the unsolvated forms for purposes of the invention.

Certain tricyclic compounds will be acidic in nature, e.g. those compounds which possess a carboxyl or phenolic hydroxyl group. These compounds may form pharmaceutically acceptable salts. Examples of such salts may include sodium, potassium, calcium, aluminum, gold and silver salts. Also contemplated are salts formed with pharmaceutically acceptable amines such as

ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine and the like.

Certain basic tricyclic compounds also form pharmaceutically acceptable salts, e.g., acid addition salts. For example, the pyrido-nitrogen atoms may form salts with strong acid, while compounds having basic substituents such as amino groups also form salts with weaker acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium hydroxide, potassium carbonate, ammonia and sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and base salts are otherwise equivalent to their respective free base forms for purposes of the invention.

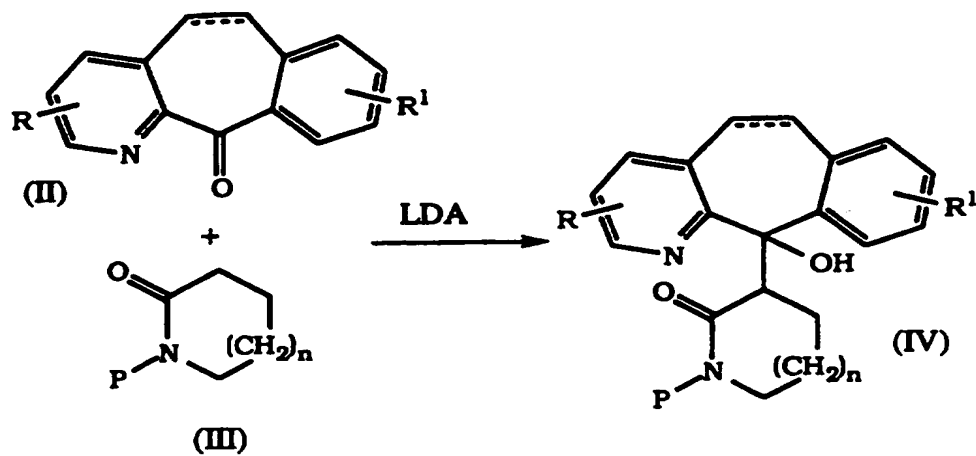
All such acid and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

The following compounds and reagents are referred to herein the abbreviations indicated: trifluoroacetic anhydride (TFAA); 4-dimethylaminopyridine (DMAP); methanol (MeOH); ethanol (EtOH); diethyl ether (Et₂O); triethylamine (Et₃N); ethyl acetate (EtOAc); acetic acid (HOAc); m-chloroperbenzoic acid (MCPBA); dicyclohexylcarbodiimide (DCC); 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (DEC); 1-hydroxy-benzotriazole (HOBt); N-methylmorpholine (NMM); dimethyl-formamide (DMF)

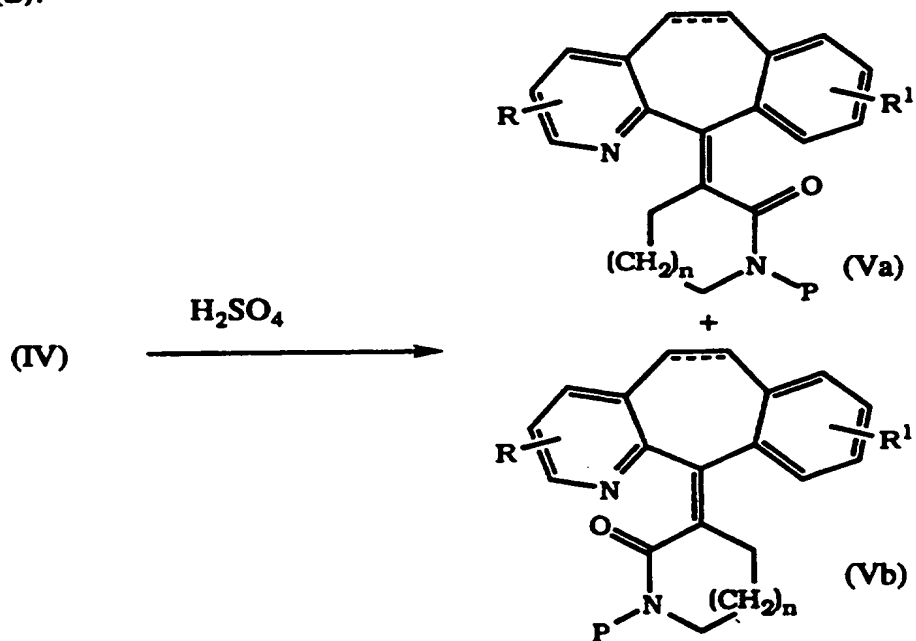
Compounds of the formula (Ia) and (Ib) can be prepared by the process shown in Reaction Scheme 1.

REACTION SCHEME 1

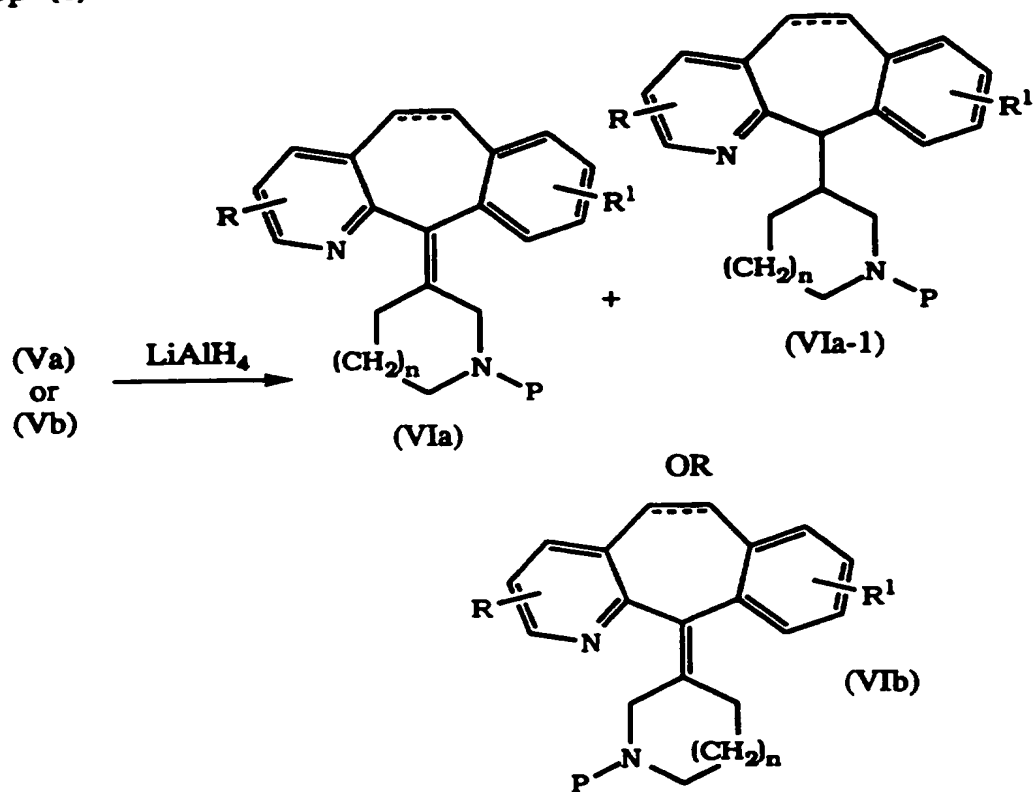
Step (a)



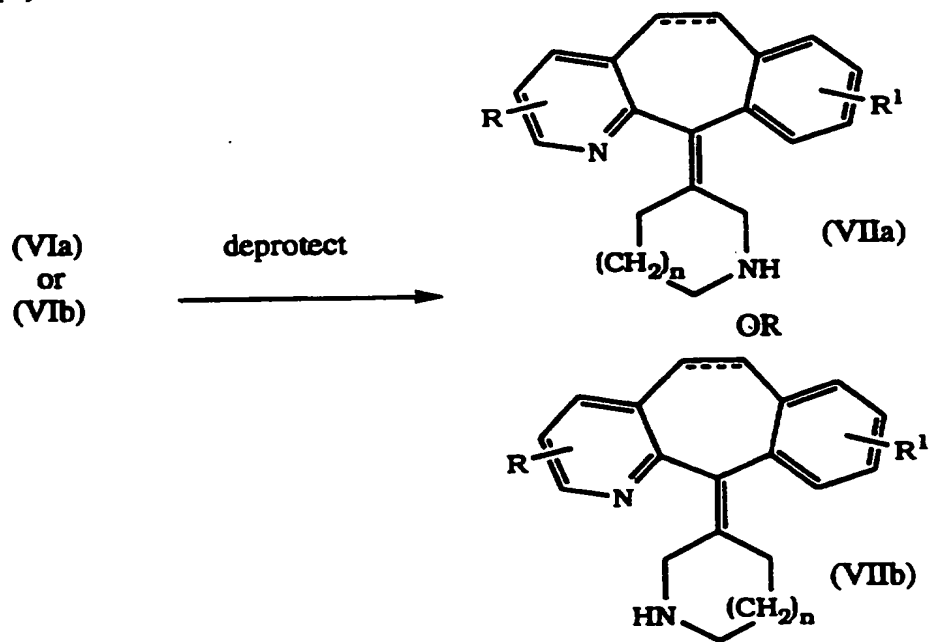
Step (b):



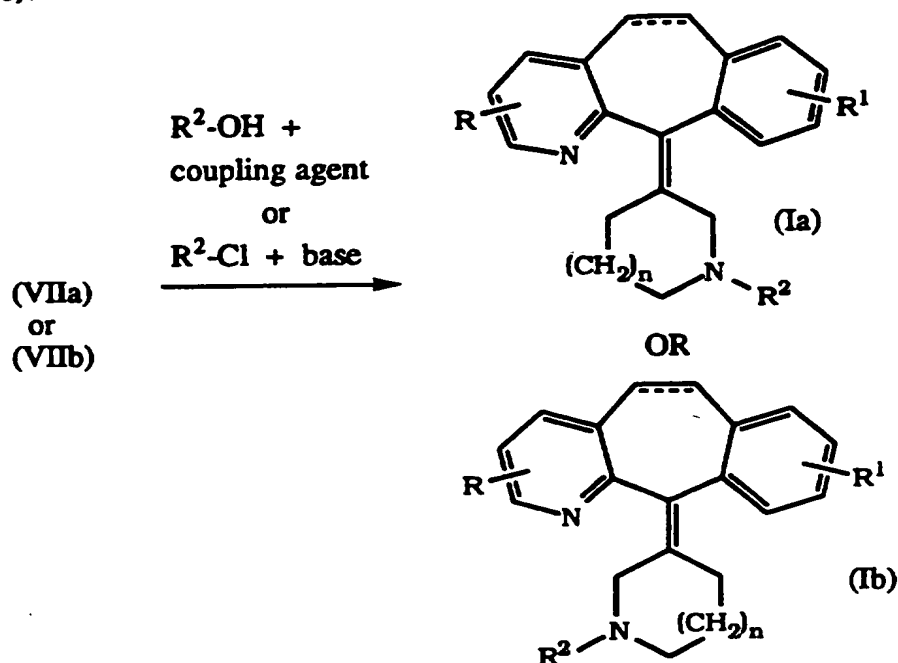
Step (c):



Step (d):



Step (e):



In Step (a) of Reaction Scheme 1, A protected lactam of the formula (III), wherein P is an amine protecting group, such as CH₃, benzyl or C₆H₅SO₂-, and n is as defined above, is treated with LDA, then reacted with a ketone of the formula (II) wherein R and R¹ are as defined above and the dotted line represents an optional double bond, at -100° to 0°C, preferably at -80° to -20°C, to form an alcohol of the formula (IV).

In Step (b) the alcohol (IV) from Step (a) is dehydrated by treating with concentrated H₂SO₄ to form a mixture of isomeric compounds (Va) and (Vb). The compounds (Va) and (Vb) are separated, e.g. by column chromatography, and a single isomer (Va) or (Vb) is used in Step (c).

In Step (c) the compound (Va) or (Vb) is treated with LiAlH₄, at -40° to 40°C, preferably at -10° to 20°C, and most preferably at about 0°C, in a suitable solvent, such as THF or Et₂O, to form a mixture compounds of the formula (VIa) and (VIa-1), or a compound of the formula (VIb), respectively.

In Step (d) the compound (VIa) or (VIb) is deprotected using reagents and reaction conditions appropriate for the specific protecting group (P), such as those described in Greene, *et al.*, "Protective Groups in Organic Synthesis, 2nd Ed.", pages

315-385, John Wiley & Sons, New York (1991), to form an amine of the formula (VIIa) or (VIIb), respectively.

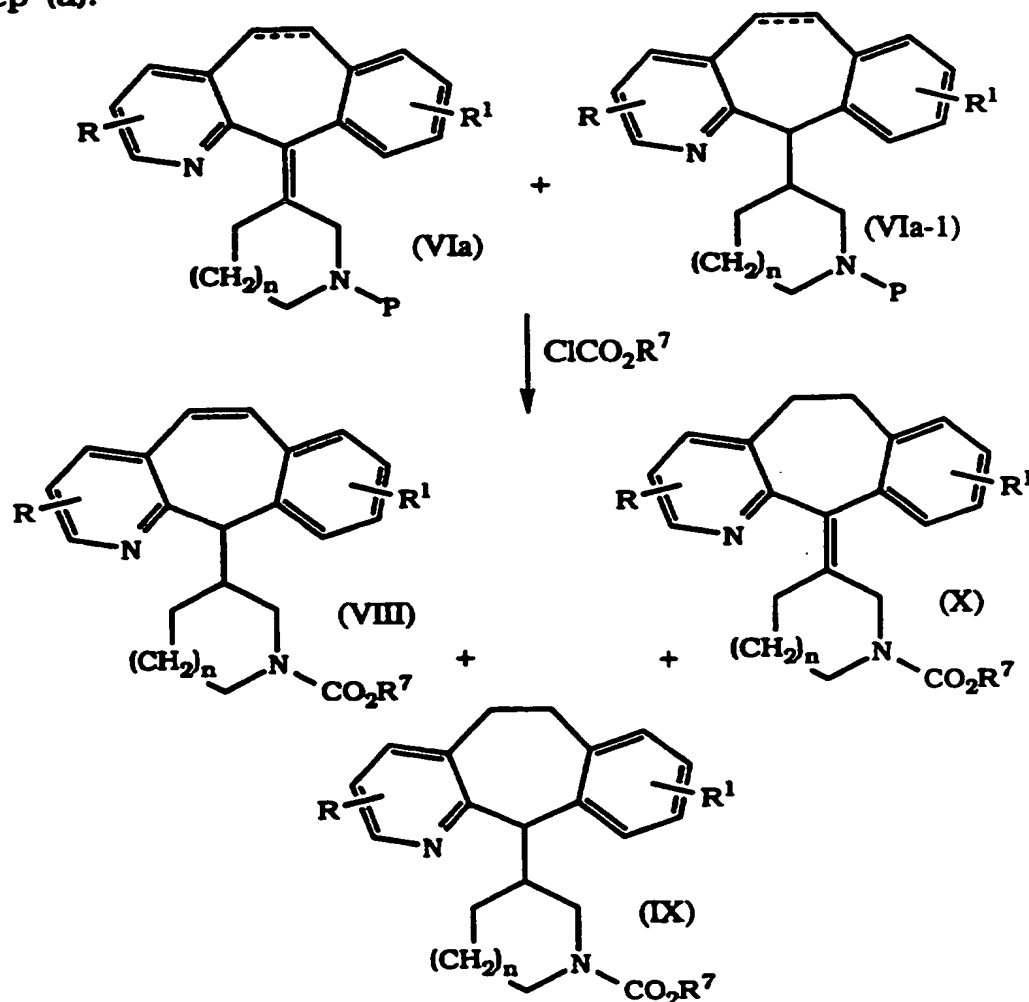
In Step (e) the amine (VIIa) or (VIIb) is reacted with a compound of the formula R^2-OH , wherein R^2 is as defined above, in a suitable solvent, such as DMF or CH_2Cl_2 , in the presence of a coupling agent, such as DCC or DEC, to form a compound of the formula (Ia) or (Ib), respectively.

Alternatively, the amine (VIIa) or (VIIb) is reacted with a compound of the formula R^2-Cl , wherein R^2 is as defined above, in the presence of a tertiary amine base, such as DMAP or pyridine, to form a compound of formula (Ia) or (Ib), respectively.

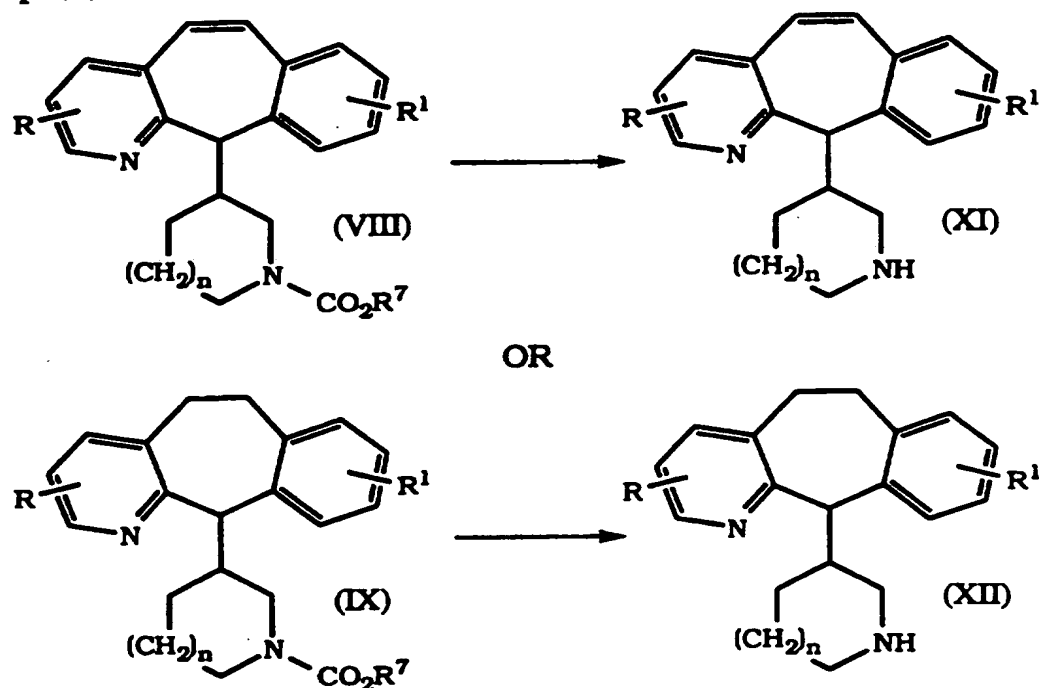
Compounds of the formula (Ic) can be prepared by the process shown in Reaction Scheme 2.

REACTION SCHEME 2

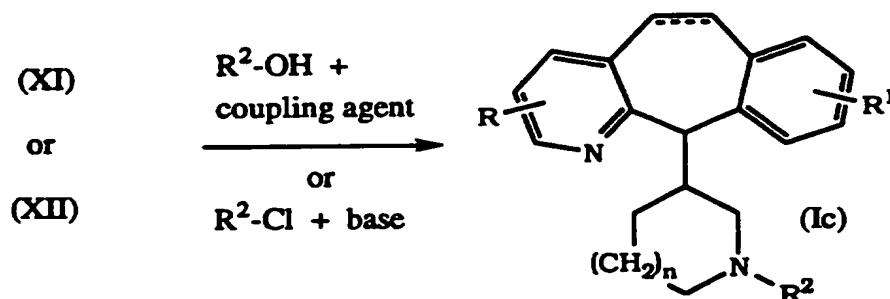
Step (a):



Step (b):



5 Step (c):



- In Step (a) of Reaction Scheme 2 the mixture of compounds of the formula (VIa) and (VIa-1) from Step (c) of Reaction Scheme 1, wherein P is CH₃, and R, R¹ and n are as defined above, and the optional double bond is not present, is reacted with a compound of the formula ClCO₂R⁷, wherein R⁷ is (C₁-C₆)alkyl, (i.e. an alkyl chloroformate), preferably ethyl chloroformate, in the presence of a tertiary amine base, preferably Et₃N, in a suitable solvent, such as toluene, at 40° to 110°C, preferably at 70° to 90°C, to form a mixture of compounds (VIII), (IX) and (X). (Compounds (VIII) and (X) are formed from compound (VIa) while compound (IX) is formed from compound (VIa-1).) Compounds (VIII), (IX) and (X) are separated, e.g. by chromatography.

In Step (b) a compound of the formula (VIII) or (IX) is reacted with concentrated HCl at 40 to 110°C, preferably at 70° to 90°C, to form an amine of the formula (XI) or (XII).

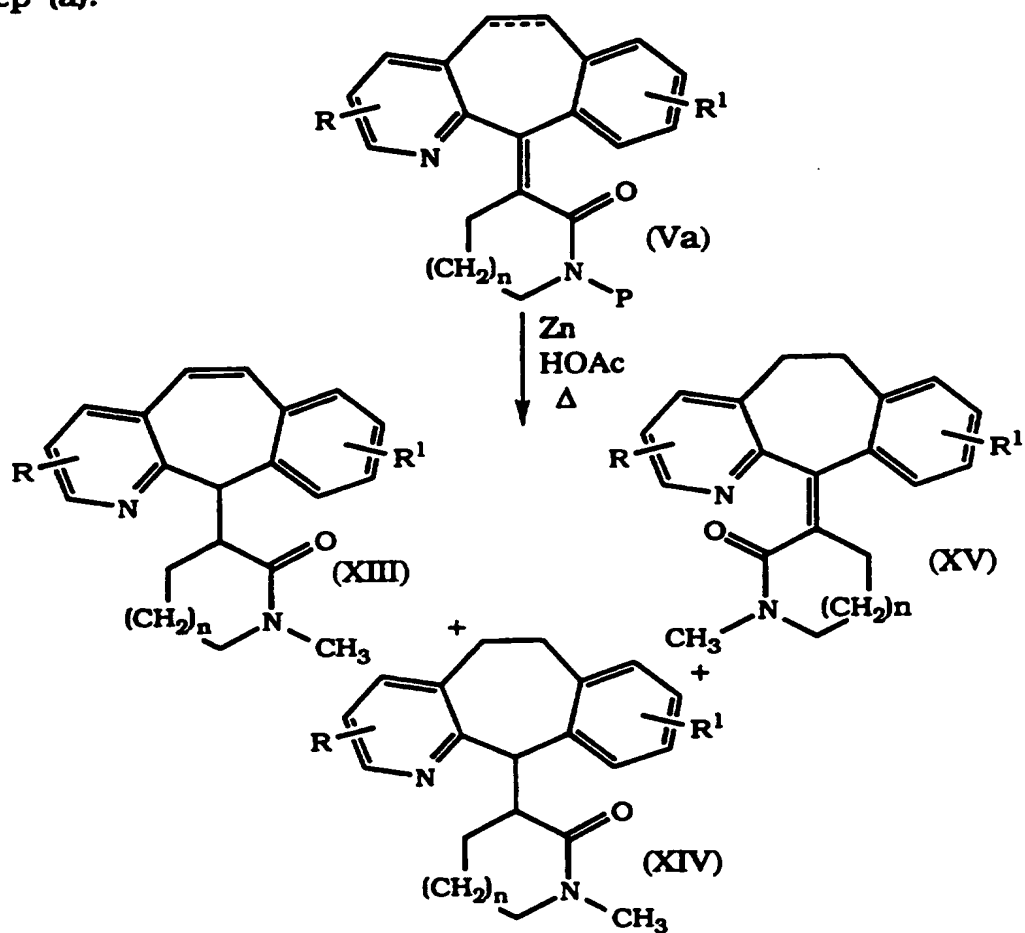
Alternatively, in Step (b) a compound of the formula (VIII) or (IX) is reacted with a hydroxide base, such as NaOH or KOH, preferably KOH, in the presence of a suitable solvent, such as a mixture of a C₁-C₆ alcohol and water, preferably a mixture of EtOH and water or iPrOH and water, at 40° to 100°C, preferably at 50° to 80°C, to form a compound of the formula (XI) or (XII), respectively.

In Step (c) a compound of the formula (XI) or (XII) is reacted with either R²OH and a coupling agent, or R²Cl and a base, via substantially the same procedures as described for Scheme 1, Step (e), to form a compound of the formula (Ic).

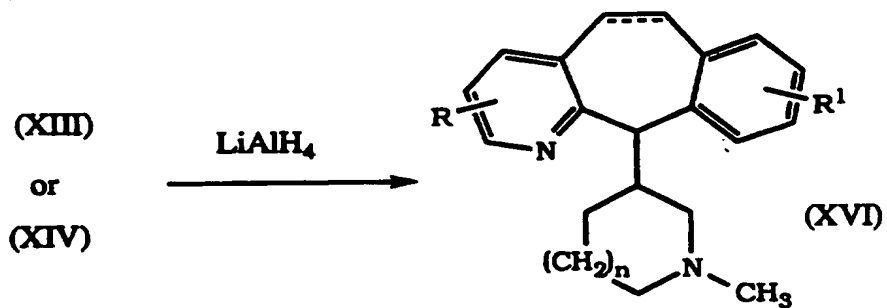
An alternative process for preparing compounds of the formula (Ic) is described in Reaction Scheme 3.

REACTION SCHEME 3

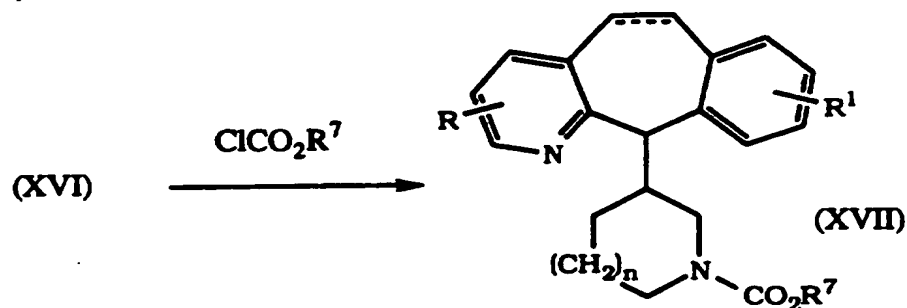
Step (a):



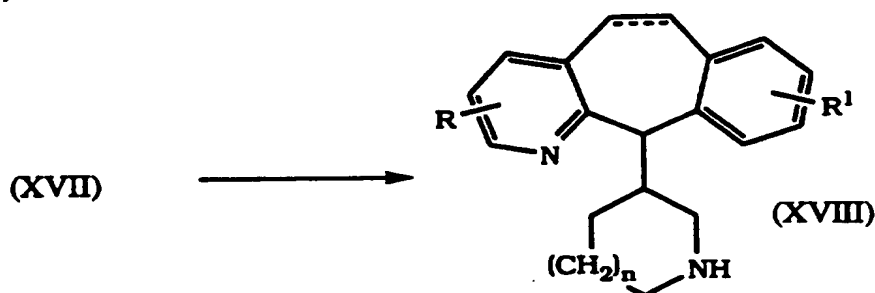
Step (b):



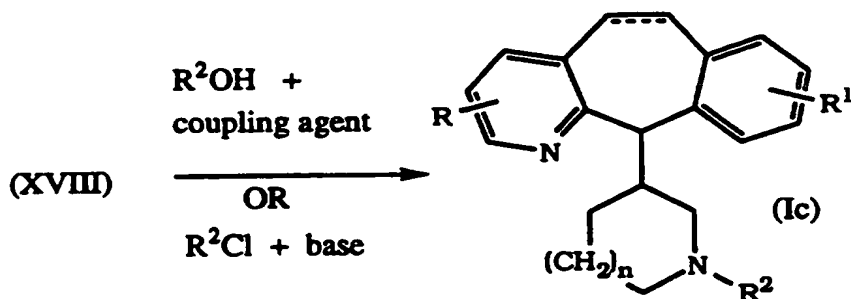
Step (c):



Step (d):



5 Step (e):



In Step (a) of Reaction Scheme 3, a compound of the formula (Va) from Step (b) of Reaction Scheme 1, wherein P is CH₃, and R, R¹ and n are as defined above, and the optional double bond is not present, is reacted with Zn powder and glacial HOAc at 80° to 120°C, preferably at about 100°C, to form a mixture of compounds (XIII), (XIV) and (XV). Compounds (XIII), (XIV) and (XV) are separated, e.g. by chromatography.

In Step (b) of Reaction Scheme 3, a compound of the formula (XIII) or (XIV) is reduced by treating with a hydride reducing agent, such as LiAlH₄, via substantially the same procedure as described for Step (c) of Reaction Scheme 1 to form a compound of the formula (XVI), wherein R, R¹ and n are as

defined above, and the dotted line represents an optional double bond.

In Step (c), a compound of the formula (XVI) is treated with a compound of the formula ClCO_2R^7 , wherein R^7 is as defined
5 above, via substantially the same procedure as described for Step (a) of Reaction Scheme 2 to form a compound of the formula (XVII).

In Step (d), a compound of the formula (XVII) is hydrolyzed via substantially the same procedure as described for Step (b) of
10 Reaction Scheme 2 to form an amine of the formula (XVIII).

In Step (e), an amine of the formula (XVIII) is reacted with either R^2OH and a coupling agent, or R^2Cl and a base, via substantially the same procedures as described for Reaction
15 Scheme 1, Step (e), to form a compound of the formula (Ic).

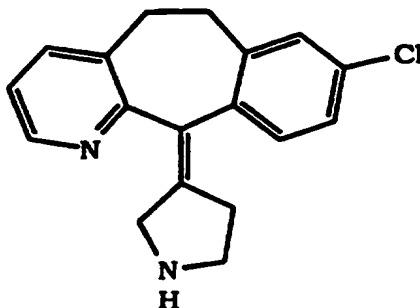
Starting ketones of the formula (II) and starting compounds of the formula (III) are known or can be prepared via known methods. Compounds of the formula R^2OH , R^2Cl and ClCO_2R^7 are known and are either commercially available or can be prepared via established methods.

20 In the above processes, it is sometimes desirable and/or necessary to protect certain R^1 , R^2 , R^3 and R^4 etc., groups during the reactions. Conventional protecting groups are operable as described in Greene, *et al.*, "Protective Groups in Organic Synthesis, 2nd Ed.", John Wiley & Sons, New York,
25 (1991). For example, see Table 1 on page 60 of WO 95/10516.

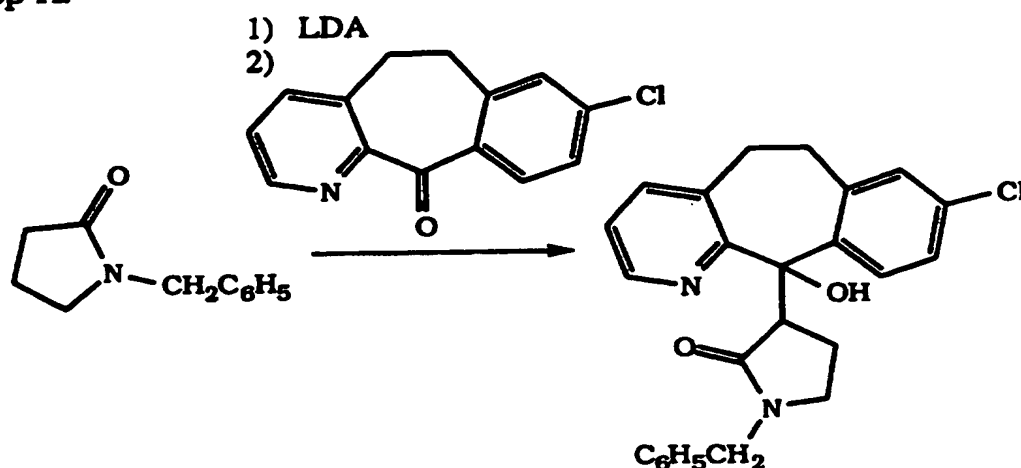
Compounds useful in this invention are exemplified by the following preparative examples, which should not be construed to limit the scope of the present invention.

30

PREPARATION 1



Step A:



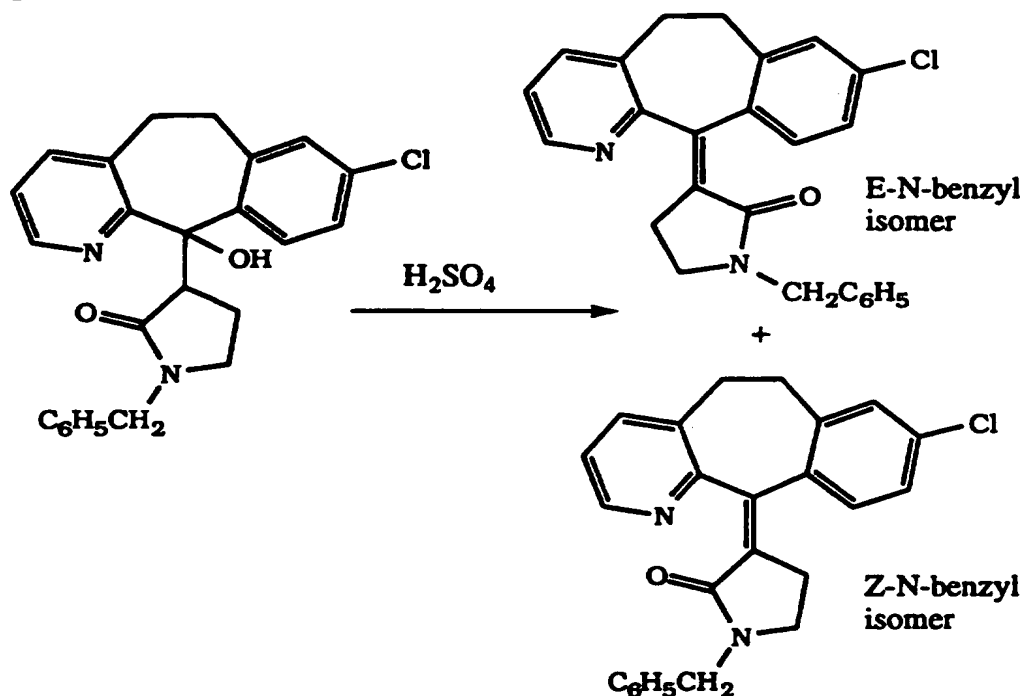
- In a flame dried 2-neck flask combine THF (400mL) and dry diisopropyl amine (0.135 mol, 13.74 g, 19.0 mL). Cool the solution to -78°C and slowly add (dropwise) *n*-BuLi (2 M, 0.134 mol, 67 mL) over 5 min. Stir the resulting mixture at -78°C for 45 min, then slowly add (dropwise) a THF solution of the lactam (0.123 mol, 21.6 g, 20 mL) over 5 min. Stir the reaction mixture at -78°C for 1h, then raised to 0°C for 1h, to give an opaque red solution. Cool the reaction mixture back down to -78°C and add a THF solution of the ketone (0.123 mol, 30 g in 300 mL THF) via cannula. When the reaction is complete by TLC analysis (after about 2 hours), raise the temperature to -50°C for 30 min, then add saturated NH_4Cl (aqueous) to quench. Dilute the mixture with additional H_2O and extract repeatedly with EtOAc. Combine the extracts and wash with brine. Dry the extracts over Na_2SO_4 , filter, and concentrate *in vacuo* to give a mixture of diastereomeric alcohols. Heat the mixture in EtOAc to give 19.9 g (42% yield) of the upper R_f diastereomer as a solid.
- Chromatograph (silica gel, 2% THF: CH_2Cl_2 increasing gradually to 5% THF: CH_2Cl_2) the material obtained from the mother liquor to give 21.3 g (45 % yield) of the lower R_f diastereomer as a solid, and 2.9 g of unreacted ketone.

Analytical data for the upper R_f diastereomer: MS (CI, $\text{M}+\text{H}$) = 385, MP $164\text{--}166^{\circ}\text{C}$. Combustion Analysis Calc: C, 71.51; H, 5.76; N, 6.67; Cl, 8.44. Found: C, 71.55; H, 5.58; N, 6.67; Cl, 8.49.

- 17 -

Analytical data for the lower R_f diastereomer: MS (CI, $M+H$) = 385, Combustion Analysis Calc: C, 71.51; H, 5.76; N, 6.67; Cl, 8.44. Found: C, 71.46; H, 5.57; N, 6.66; Cl, 8.40.

Step B:



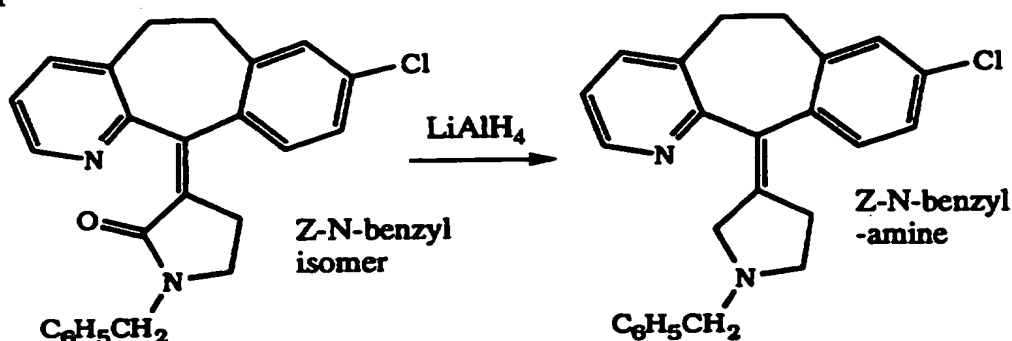
5

Combine 1.0 g (2.38 mmol) of the upper R_f diastereomer from Step A and concentrated H_2SO_4 at room temperature. Heat the mixture to $60^\circ C$ for 1.5 h, then cool to room temperature and poured into crushed ice. Basify the resulting solution to a pH of about 10 with 10% NaOH (aqueous) and extract repeatedly with CH_2Cl_2 (or EtOAc). Combine the extracts, wash the extracts with brine, then dry over Na_2SO_4 , filtered and concentrate *in vacuo* to a residue. Chromatograph (silica gel, 5% acetone: CH_2Cl_2 increasing gradually to 5% MeOH: CH_2Cl_2) to give 200 mg of the E-N-benzyl isomer, and 600 mg of the Z-N-benzyl isomer as solids.

10 Analytical data for the E-N-benzyl isomer: MS (CI, $M+H$) = 401, MP $178-180.5^\circ C$. Combustion Analysis Calc: C, 74.90; H, 5.28; N, 6.99; Cl, 8.84.

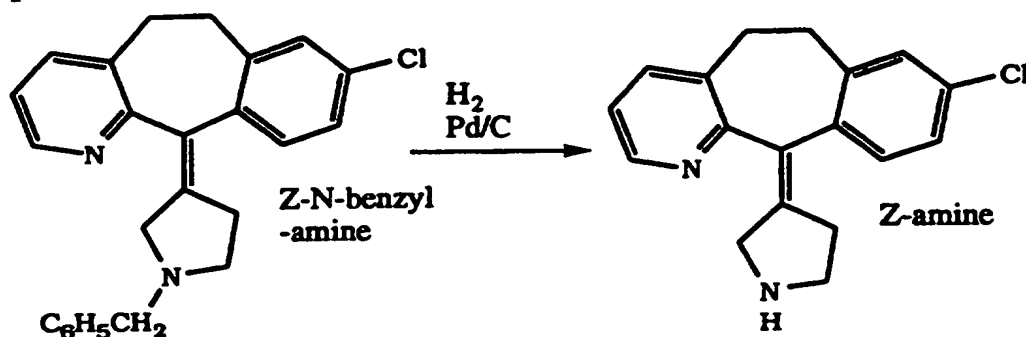
20 Analytical data for the Z-benzyl isomer: MS (CI, $M+H$) = 401, Combustion Analysis Calc: C, 74.90; H, 5.28; N, 6.99; Cl, 8.84. Found: C, 74.78; H, 5.41; N, 6.97; Cl, 8.82.

Step C:



- Combine the Z-N-benzyl isomer from Step B and 5 mL of THF under a N₂ atmosphere. Cool the solution to 0°C, and add
- 5 70 mg of LiAlH₄ (1.867 mmol) in portions. Stir the mixture for about 30 min. at 0°C, then quench with EtOAc and MeOH. Filter through celite® to remove the aluminum salts, concentrate the filtrate and add 5% NaOH (aqueous). Extract the aqueous portion with EtOAc:THF (9:1), combine the organic phases and wash with
- 10 brine. Dry over Na₂SO₄, filter and concentrate the filtrate *in vacuo* to a residue. Chromatograph (silica gel, 10% acetone:hexane increasing gradually to 20% acetone:hexane) to give 175 mg (51% yield) of the Z-N-benzylamine. Analytical data for the Z-N-benzylamine: MS (CI, M+H) = 387. High resolution MS Calc. for
- 15 C₂₅H₂₄N₂Cl: 387.1628. Found: 387.1609.

Step D:

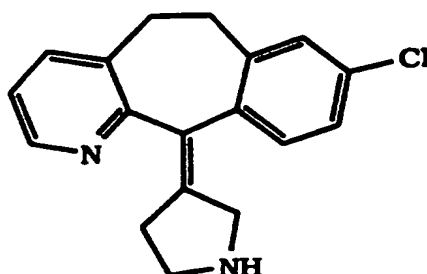
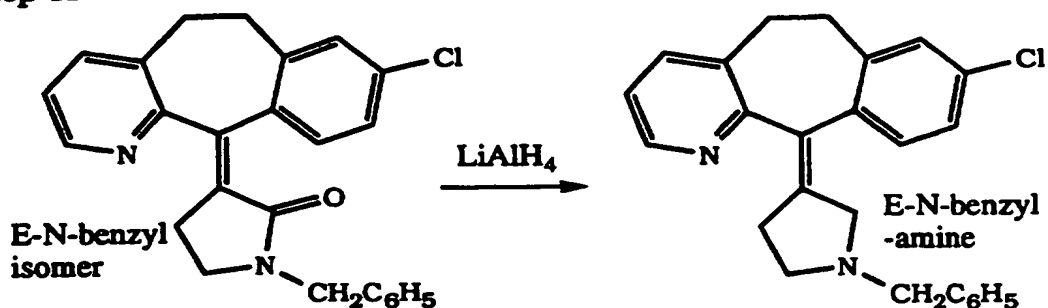


- Combine 500 mg of the Z-N-benzylamine from Step C (1.29 mmol), MeOH (20 mL), HOAc (5 mL), 1,4-cyclohexadiene (5 mL) and 210 mg of 10% Pd/C under N₂ atmosphere. Carefully heat the mixture to 70°C at which time hydrogen evolution began. After 1 hour and add hydrogen and continue heating at about 40°C for an additional 1h. Filter the mixture through celite®, and concentrate the filtrate *in vacuo* to a residue. Add toluene and concentrate *in vacuo* again to remove residual HOAc. Chromatograph (silica gel, 5% MeOH:CH₂Cl₂ increasing gradually to 10% MeOH:CH₂Cl₂:1% NH₄OH) to give 221 mg (58 % yield) of the Z-amine product (P-1). Analytical data for Z-amine: MS (CI, M+H) = 296.

- Using the starting ketone indicated and following substantially the same procedure as described in Preparation 1, the following amine was prepared:

Starting Ketone	Amine
	<p style="text-align: right;">(P-1A)</p>

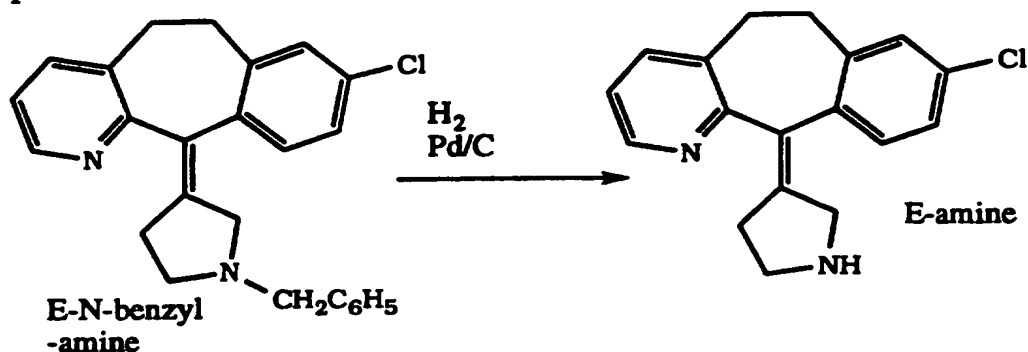
- 20 -

PREPARATION 2**Step A**

- 5 Combine 1.04 g of LiAlH_4 (27.7 mmol) and 75 mL of Et_2O under a N_2 atmosphere. Cool the mixture to 0°C , and add a THF solution of 2.20 g (5.49 mmol) of the E-N-benzyl isomer from Step B of Preparation 1, via syringe. After 120 min., quench the reaction mixture with EtOAc and MeOH, followed by the addition
- 10 of 1% NaOH (aqueous). Extract the aqueous portion with EtOAc (4 X 75 mL), then with EtOAc:THF (4:1), and combine the extracts. Wash the extracts with brine, dry over MgSO_4 , filter and concentrate *in vacuo* to a residue. Chromatograph (silica gel, 15% acetone:EtOAc increasing gradually to 5% MeOH:EtOAc) to give
- 15 1.08 g (51% yield) of the E-N-benzylamine product.

Analytical data for the E-N-benzylamine: MS (CI, $\text{M}+\text{H}$) = 387, Combustion Analysis Calc: C, 77.61; H, 5.99; N, 7.24; Cl, 9.16. Found: C, 77.80; H, 6.07; N, 7.20; Cl, 8.94.

Step B:

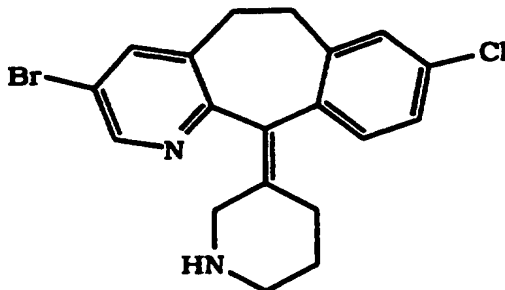


The E-N-benzylamine from Step A is hydrogenated using Pd/C via essentially the same procedure as described for the Z-isomer in Step D of Preparation 1 to give the E amine product (P-2).

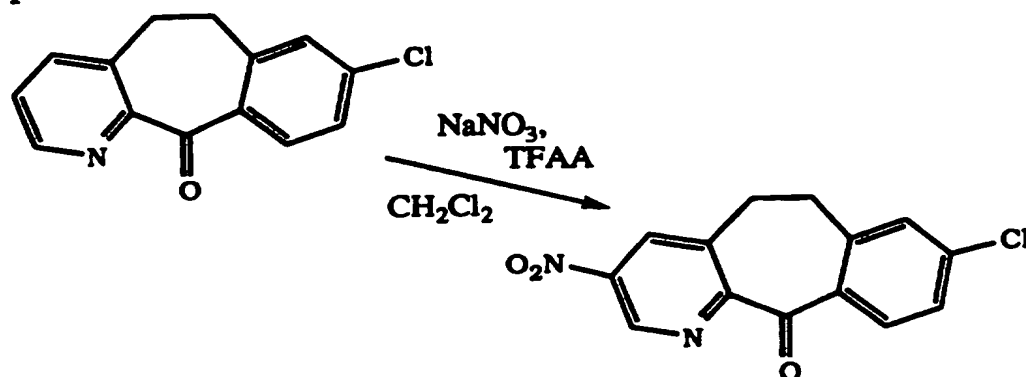
Using the starting ketone indicated and following substantially the same procedure as described in Preparation 2, the following amine was prepared:

Starting Ketone	Amine
	<p>(P-2A)</p>

10

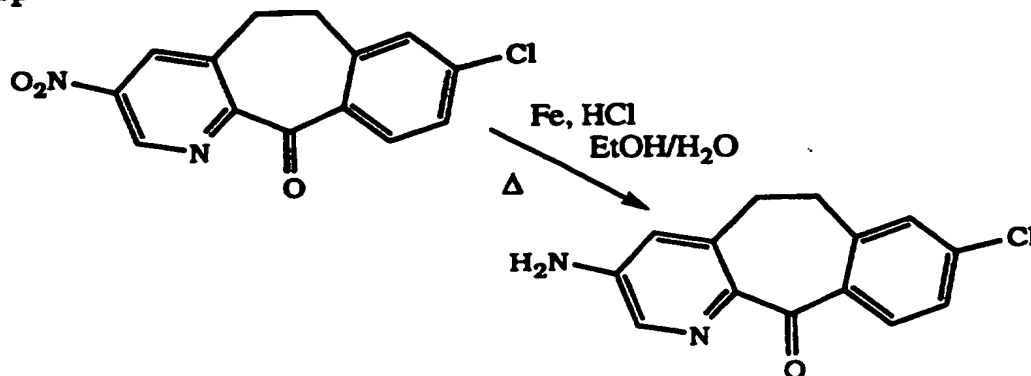
PREPARATION 3

Step A:



- Combine 10 g (41.03 mmol) of the ketone and 100 mL of CH_2Cl_2 and cool to -5°C . Add 7.0 mL (49.5 mmol) of TFAA, then
- 5 add 3.7 g (43.53 mmol) NaNO_3 to the stirred mixture. Allow the mixture to warm to 20°C and stir for 30 hours. Cool the mixture to 0°C and slowly add a solution of 30 mL of concentrated NH_4OH (aqueous) in 100 mL of water. Stir for 30 min. then add 300 mL
- 10 of CH_2Cl_2 and 200 mL of water. Separate the layers and dry the organic phase over MgSO_4 . Filter and concentrate *in vacuo* to a solid residue. Stir the solid in 100 mL of hot MeOH for 30 min. then allow the mixture to cool to room temperature. Filter, wash the solid with 20 mL of MeOH and dry under vacuum (0.2 mm Hg) at room temperature to give 4.9 g (41.4% yield) of the
- 15 nitroketone product.

Step B:



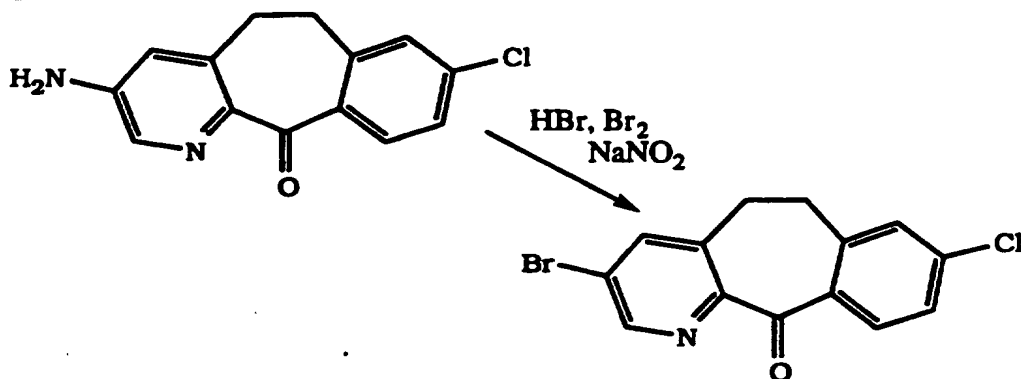
- Combine 5 g (17.3 mmol) of the nitroketone from Step A, 140 mL of EtOH and 15 mL of water at room temperature, then
- 20 add 3 g (54.5 mmol) of Fe powder. Add 1 mL of concentrated HCl and heat the mixture at reflux for 4 hours. Cool the mixture to room temperature and concentrate *in vacuo* to a volume of about

- 23 -

- 20 mL. Add 100 mL of water, 200 mL of CH_2Cl_2 and 30 mL of 20% NaOH (aqueous). Separate the layers and extract the aqueous phase with 200 mL of CH_2Cl_2 . Combine the organic extracts, filter and wash with 100 mL of water. Dry over MgSO_4
- 5 then concentrate *in vacuo* to a residue. Stir the residue in a mixture of 20 mL of acetone and 100 mL Et_2O to form a solid. Filter and wash the solid with 20 mL of Et_2O , then dry *in vacuo* at 20°C to give 4.0 g (89.5% yield) of the aminoketone product.

- Analytical data for the aminoketone: m.p.= $199^\circ\text{--}200^\circ\text{C}$; MS (CI) = 259, 261; Combustion analysis: calc. - C, 64.99; H, 4.28; N, 10.83, found - C, 64.79; H, 4.41; N, 10.58.
- 10

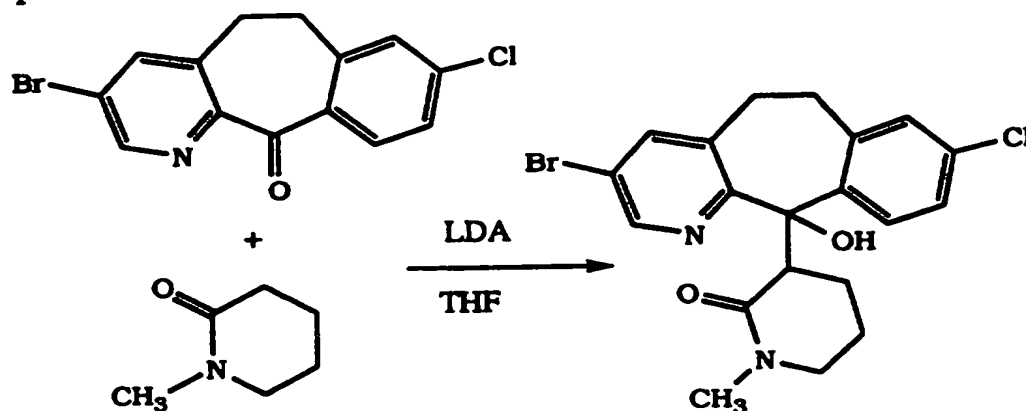
Step C:



- Combine 10 g (0.386 mole) of the aminoketone from Step B
- 15 and 300 mL of 48% HBr at -5°C , then add 9.0 mL (1.74 mole) of Br_2 and stir at -5°C for 20 min. Slowly add (dropwise) a solution of 10.5 g (1.52 mole) NaNO_2 in 25 mL of water, keeping the temperature at -5°C . Stir for 1 hour at -5°C , allow the mixture to warm to 20°C over 1 hour and stir at 20°C for 4 hours. Pour the
- 20 mixture into 300 g of ice, and add 40% NaOH (aqueous) to the ice cold mixture to adjust to $\text{pH} = 14$. Extract with CH_2Cl_2 (2 X 300 mL), combine the extracts and dry over MgSO_4 . Filter and concentrate *in vacuo* to a residue. Chromatograph the residue (silica gel, 25% EtOAc /hexanes) to give 8.7 g (69.9%
- 25 yield) of the bromoketone product.

Analytical data for the bromoketone: MS (CI) = 322, 324.

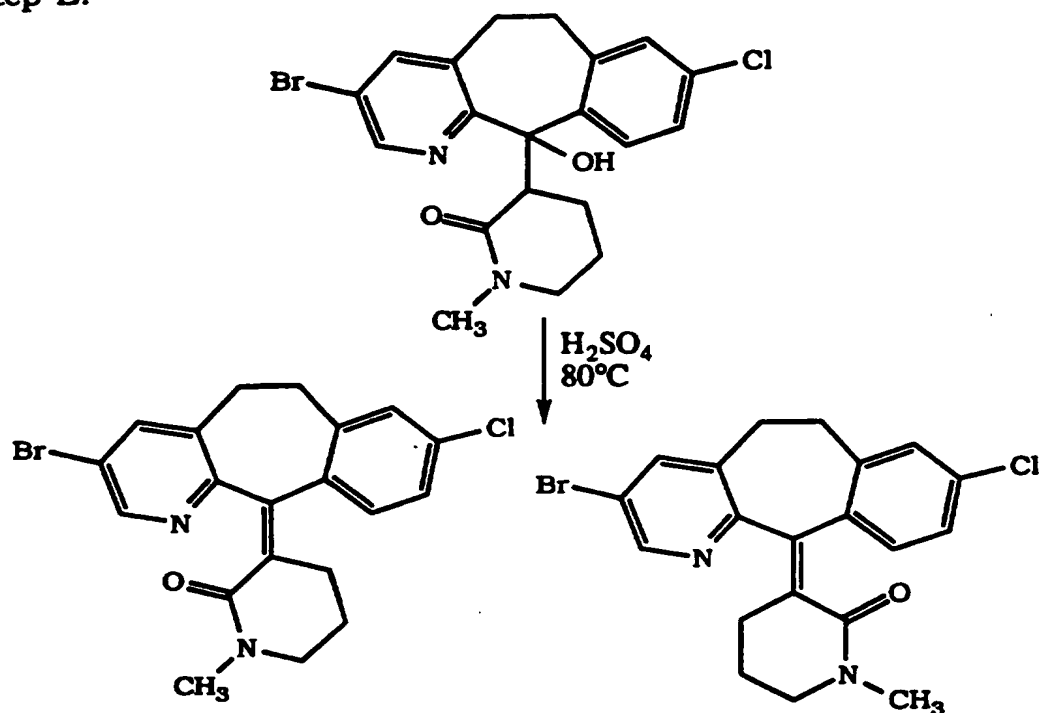
Step D:



- Slowly add (dropwise) 18 mL (45.0 mmol) of 2.5 M n-butyllithium in hexanes to a solution of 7.0 mL (49.41 mmol) diisopropylamine in 100 mL of THF at -78°C. Stir at -78°C for 15 min. then add 7.0 mL (64 mmol) of N-methyl-2-piperidone. Stir the mixture at -78°C for 30 min. then warm to -5°C over a 1 hour period. Cool to -78°C and slowly add (dropwise) a solution of 12 g (37.2 mmol) of the bromoketone from Step C in 200 mL of dry THF. Stir the mixture at -78°C for 1 hour, then warm to -10°C over 1.5 hours. Add 25 mL of water and concentrate *in vacuo* to remove about 200 mL of the solvent. Extract with 600 mL of CH₂Cl₂ and 300 mL of brine, and dry the organic extract over MgSO₄. Filter, concentrate *in vacuo* to a residue and stir the residue in a mixture of 30 mL of acetone and 20 mL of Et₂O to form a solid. Filter, wash the solid with 10 mL of Et₂O and dry at 20°C, 0.2 mm Hg, overnight to give 11.89 g of the product as a mixture of diastereomers. Chromatograph (silica gel, 25% EtOAc/hexanes) the mother liquor and Et₂O wash to give an additional 1.0 g of the product (79.56% total yield).

Analytical data for the product of Step D: MS (CI, M+H) = 437; combustion analysis: calc. - C, 55.12; H, 4.62; N, 6.43, found - C, 54.70; H, 4.57; N, 6.26.

Step E:



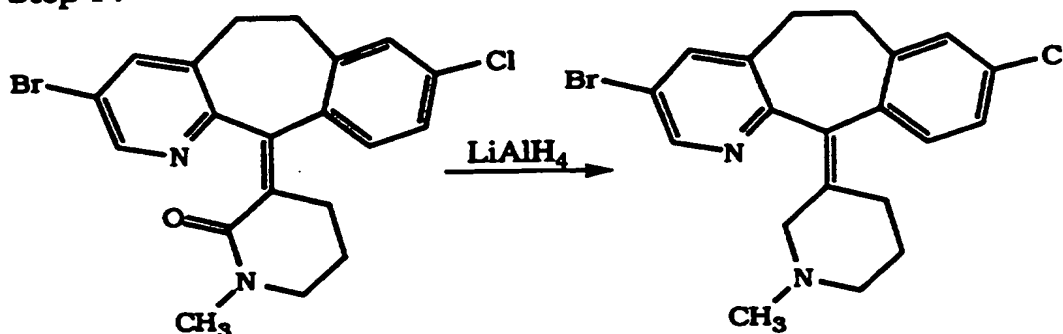
Combine 11.4 g (26.1 mmol) of the product from Step D and 100 mL of concentrated H_2SO_4 and heat to 80°C for 4 hours.

- 5 Cool the mixture to 20°C , pour into 300 g of ice and add 50% NaOH (aqueous) to the ice cold mixture to adjust to $\text{pH} = 14$. Filter to collect the resulting solid, wash the solid with 300 mL of water, then dry at 20°C , 0.2 mm Hg, overnight. Chromatograph the solid (silica gel, 2% MeOH/EtOAc) to give 4.48 g of the Z-isomer and 4.68 g of the E-isomer of the product (total yield 84%).
- 10

Analytical data for Z-isomer: MS (CI, $\text{M}+\text{H}$) = 417, 419; combustion analysis: calc. - C, 57.50; H, 4.34; N, 6.70, found - C, 57.99; H, 4.76; N, 6.66.

- 15 Analytical data for E-isomer: MS (CI, $\text{M}+\text{H}$) = 417, 419; combustion analysis: calc. - C, 57.50; H, 4.34; N, 6.70, found - C, 57.23; H, 4.43; N, 6.65.

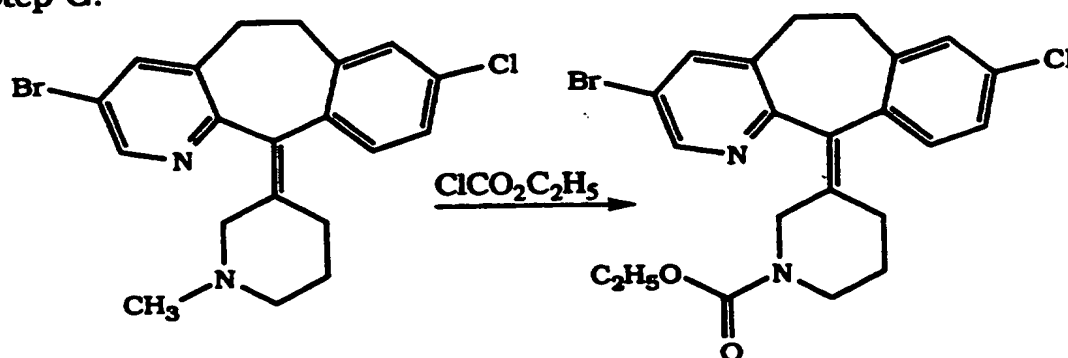
Step F:



- Combine 1.0 g (2.39 mmol) of the Z-isomer product from Step E and 10 mL of dry THF at -10°C and add 110 mg (2.78 mmol) of LiAlH_4 . Stir the mixture at -10° to -5°C for 2 hours, then add 2 mL of EtOAc followed by 20 mL of 10% potassium sodium tartrate tetrahydrate (aqueous), 5 mL of 10% NaOH (aqueous) and 150 mL of CH_2Cl_2 . Separate the layers and dry the organic phase over MgSO_4 . Filter and concentrate *in vacuo* to a residue. Chromatograph the residue (silica gel, first 25% EtOAc/hexanes, then 3% MeOH/EtOAc containing concentrated 1% NH_4OH) to give 480 mg (50% yield) of the Z-methylamine product.

- Analytical data for the Z-methylamine: m.p. = $160^\circ\text{--}161^\circ\text{C}$;
 MS (CI, $\text{M}+\text{H}$) = 403, 405; combustion analysis: calc. - C, 59.49; H, 4.99; N, 6.94, found - C, 59.75; H, 5.43; N, 6.79.

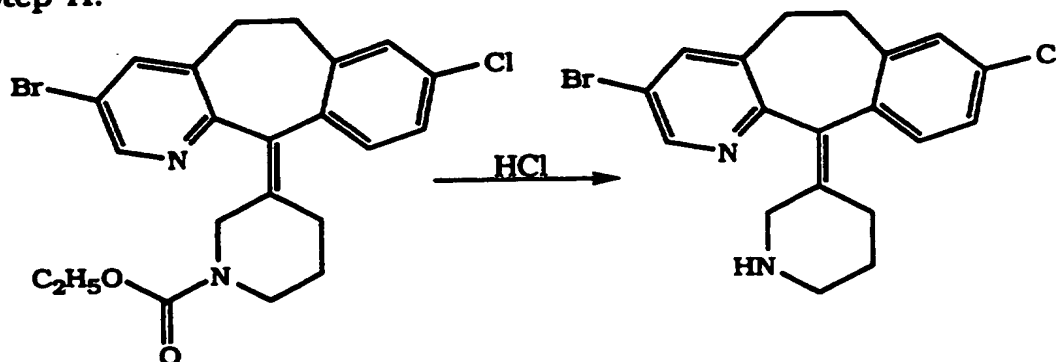
Step G:



- Combine 1.1 g (2.72 mmol) of the Z-methylamine from Step F and 20 mL of toluene at 0°C and add 1.0 mL (10.4 mmol) of $\text{ClCO}_2\text{C}_2\text{H}_5$. Add 1.0 mL (13.6 mmol) of Et_3N and heat the mixture to 70°C for 3 hours. Cool the mixture and concentrate *in vacuo* to a residue. Extract the residue with 50 mL of CH_2Cl_2 and wash the extract with 30 mL of water. Dry over MgSO_4 , filter and

concentrate *in vacuo* to a residue. Chromatograph the residue (silica gel, 20% EtOAc/hexanes) to give the crude product. Crystallize from a mixture of EtO and CH₂Cl₂ to give 510 mg (40.8% yield) of the Z-ethylcarbamate product.

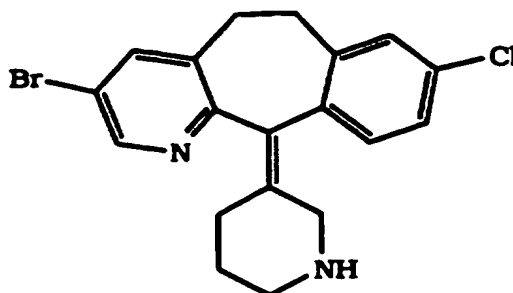
- 5 Analytical data for the Z-ethylcarbamate: m.p. = 182°-183°C; MS (CI, M+H) = 461, 463; combustion analysis: calc.- C, 57.29; H, 4.80; N, 6.06, found - C, 57.38; H, 4.72; N, 6.08.
Step H:



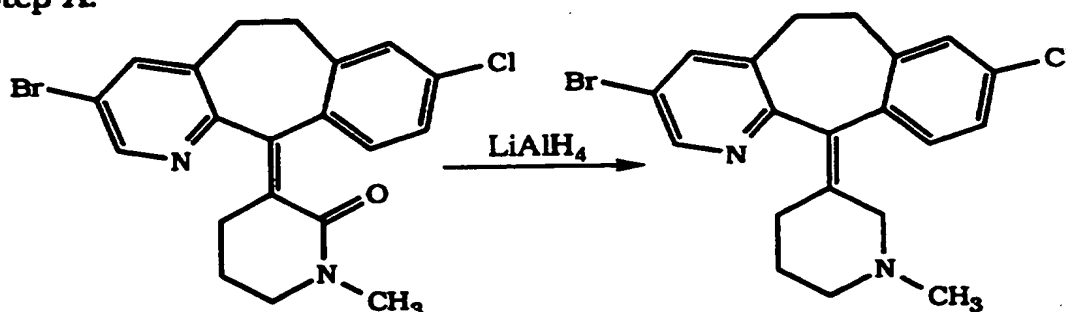
- 10 Combine 400 mg (0.866 mmol) of the Z-ethylcarbamate from Step G and 5 mL of concentrated HCl and heat at 100°C overnight. Cool to 0°C and slowly add 30% NaOH (aqueous) to basify the mixture. Extract with CH₂Cl₂ (2 X 250 mL) and dry the extract over MgSO₄. Filter and concentrate *in vacuo* to give 320 mg (94.86% yield) of the Z-amine product (P-3). Analytical data for the Z-amine (P-3): MS (FAB, M+H)= 389, 391.

Using the starting ketone indicated and following substantially the same procedure as described in Steps D to H of Preparation 3, the following amine was prepared:

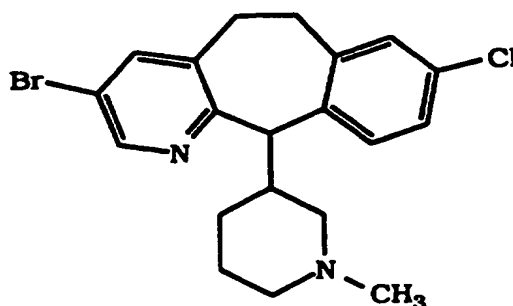
Starting Ketone	Amine
	<p>(P-3A), m.p. = 169 -170 C</p>

PREPARATION 4

Step A:



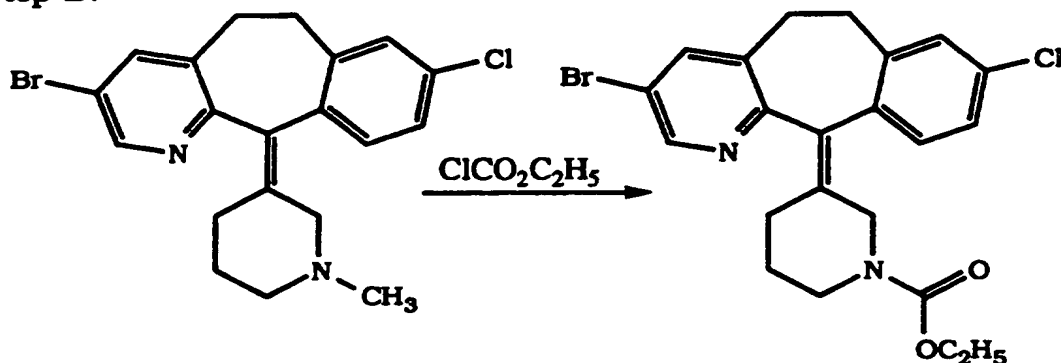
- 5 Combine 3.4 g (8.15 mmol) of the E-isomer product from Step E of Preparation 3 and 40 mL of dry THF at -5°C and add 470 mg (11.9 mmol) of LiAlH₄. Stir the mixture at 0°C for 5 hours, then add 5 mL of water, 20 mL of 10% potassium sodium tartrate tetrahydrate (aqueous), 5 mL of 10% NaOH (aqueous) and
- 10 150 mL of CH₂Cl₂. Separate the layers and dry the organic phase over MgSO₄. Filter and concentrate *in vacuo* to a residue. The residue is a mixture of the product compound and a compound of the formula



- 15 Chromatograph the residue (silica gel, 2% MeOH/EtOAc) to give 1.3 g (40% yield) of the E-methylamine product.

Analytical data for the E-methylamine: m.p.= 140°-141°C; MS (CI, M+H) = 403, 405; combustion analysis: calc. - C, 59.49; H, 4.99; N, 6.94, found - C, 59.11; H, 4.75; N, 6.98.

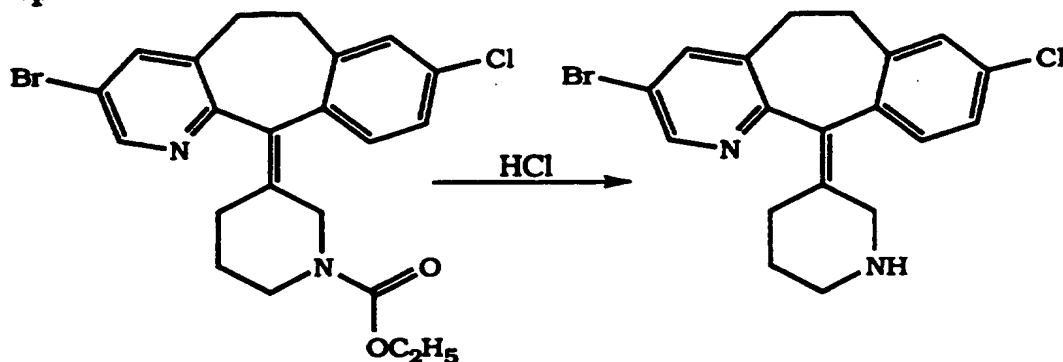
Step B:



Using 0.4 g (0.99 mmol) of the E-methylamine from Step A, 15 mL of toluene, 0.5 mL (5.2 mmol) of $\text{ClCO}_2\text{C}_2\text{H}_5$, and 0.5 mL
 5 (6.8 mmol) of Et_3N , and substantially the same procedure as described in Preparation 3, Step G, 230 mg (51.1% yield) of the E-ethylcarbamate product is prepared.

Analytical data for the E-ethylcarbamate: m.p. = 186° - 187°C ; MS (CI, $\text{M}+\text{H}$) = 463, 464; combustion analysis: calc. - C, 57.29; H, 4.80; N, 6.06, found - C, 57.43; H, 5.11; N, 6.09.
 10

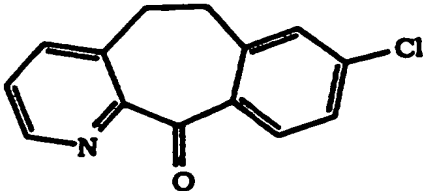
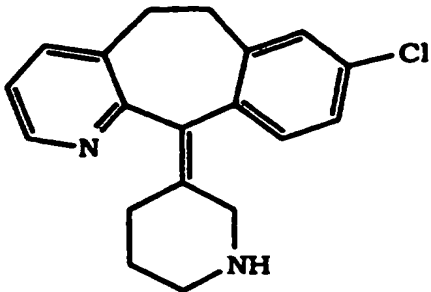
Step C:

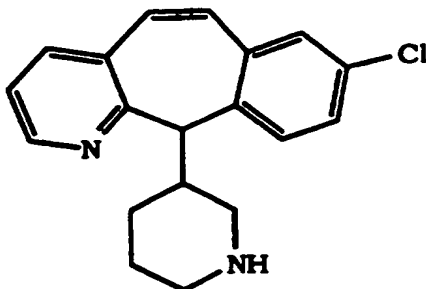
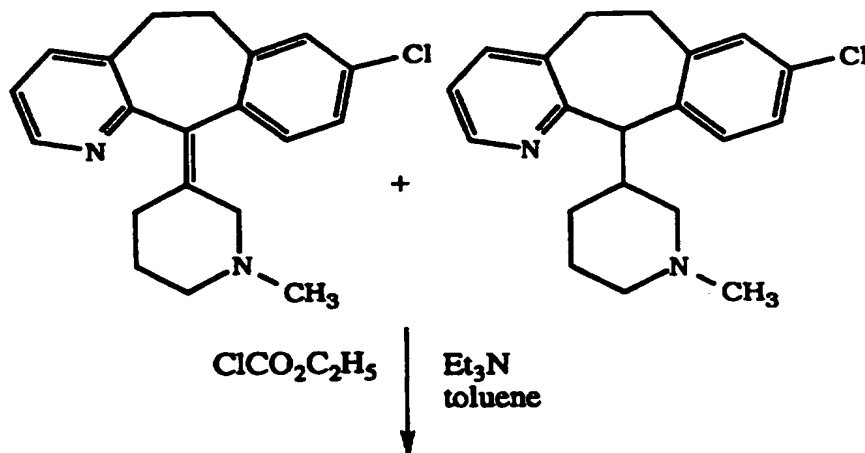


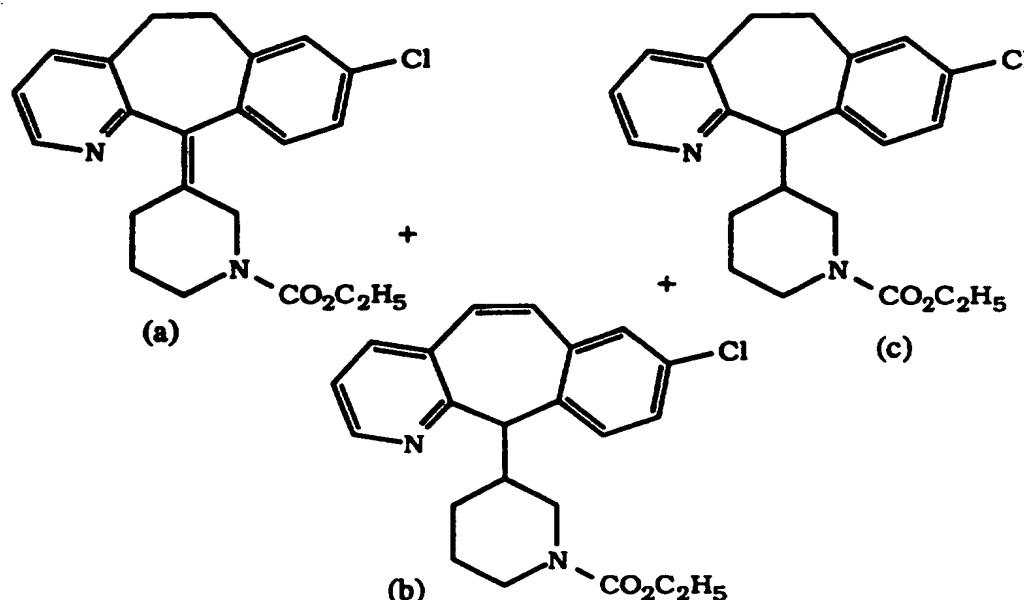
The E-ethylcarbamate from Step B is converted to the E-amine (P-4) in 97.8% yield using substantially the same procedure
 15 as described in Preparation 3, Step H.

Analytical data for the E-amine (P-4): m.p. = 166° - 167°C ; MS (CI) = 389, 391; combustion analysis: calc. - C, 57.88; H, 4.66; N, 7.10, found - C, 57.63; H, 4.61; N, 7.03.

Using the starting ketone indicated to prepare the
 20 appropriate E-isomer via the procedures described in Steps D and E of Preparation 3, Steps A-E, the following amines were prepared via substantially the same procedure as described in Steps A-C of Preparation 4:

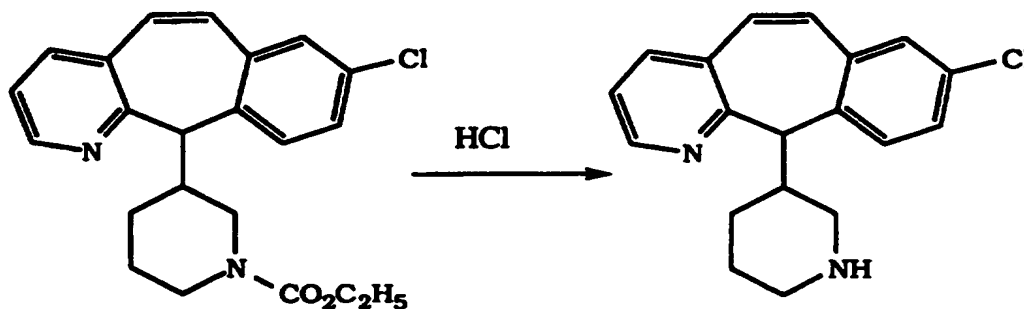
Starting Keton	Amin
	 (P-4A), m.p. = 140°-141°C

PREPARATION 5**Step A:**



- Combine 20 g (61.5 mmol) of the crude (no chromatography) E-methyl-amine obtained from Preparation 4, Step A (using the appropriate starting ketone), and 200 mL of toluene at 0°C, and add 20 mL (208 mmol) of $\text{ClCO}_2\text{C}_2\text{H}_5$. Add 20 mL (272 mmol) of Et_3N , then heat to 80°C and stir for 4 hours. Cool to room temperature and concentrate *in vacuo* to a residue. Extract the residue with 300 mL of CH_2Cl_2 , wash the extract with 200 mL of water, then dry over MgSO_4 . Filter, concentrate *in vacuo* to a residue, then chromatograph the residue (silica gel, 70% EtOAc/hexanes) to give 5.0 g of product (a), 4.2 g of product (b), and 300 mg of product (c). Analytical data: MS (CI, $\text{M}+\text{H}$) product (a) = 383, product (b) = 383, product (c) = 385.

Step B:



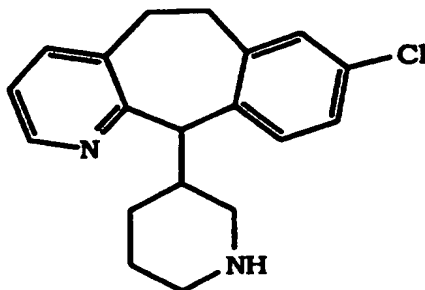
15

Combine 4.0 g (10.4 mmol) of product (b) from Step A and 20 mL of concentrated HCl and heat at 80°C overnight. Cool to 20°C, basify to $\text{pH} = 14$ with 20% NaOH (aqueous), and extract with 200 mL of CH_2Cl_2 . Wash the extract with 25 mL of water,

- 32 -

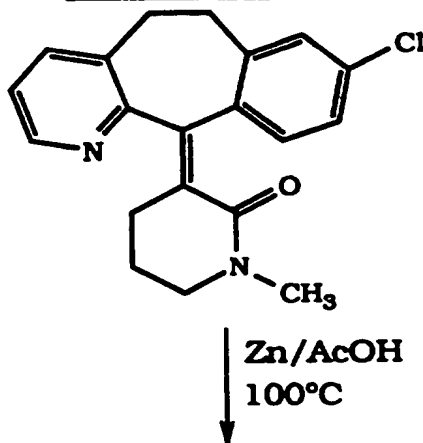
- dry over MgSO_4 , filter and concentrate *in vacuo* to a residue. Chromatograph the residue (silica gel, 10% MeOH/EtOAc + 2% NH_4OH (aqueous)), then triturate with 15 mL of acetone/ Et_2O to give 1.96 g (60.5% yield) of the amine product (P-5). Analytical data for amine (P-5): m.p.=157°-158°C; MS (CI, M+H)=311, 313.

PREPARATION 6

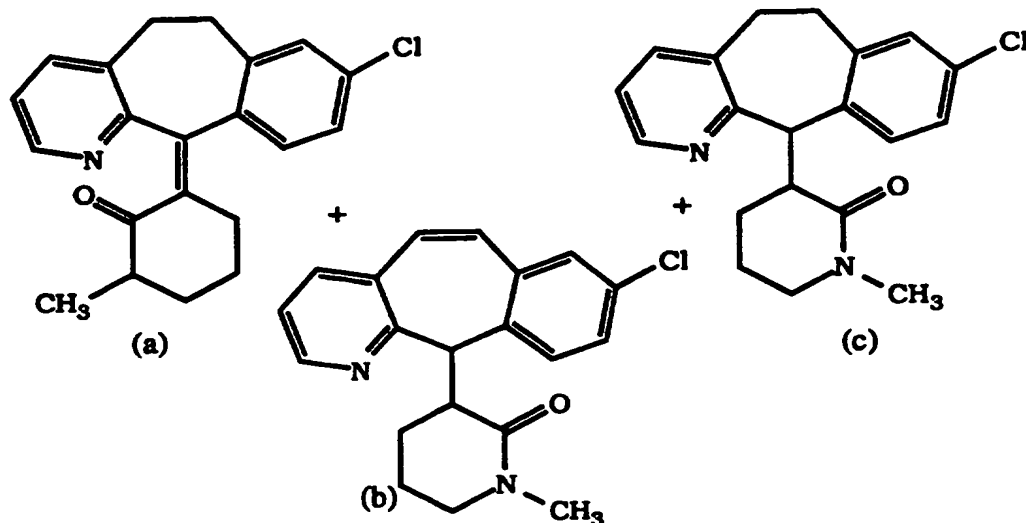


- Combine 400 mg (1.03 mmol) of product (c) from Preparation 5, Step A, and 5 mL of EtOH at 20°C, then add a solution of 0.23 g (4.15 mmol) KOH in 10 mL of water. Heat the mixture at reflux for 3 days, cool to room temperature and concentrate *in vacuo* to a residue. Extract the residue with 80 mL of CH_2Cl_2 and wash the extract with 50 mL of water. Dry over MgSO_4 , filter and concentrate *in vacuo* to a residue. Chromatograph the residue (silica gel, 10% MeOH/EtOAc + 2% NH_4OH (aqueous)), then triturate with 10 mL of Et_2O to give 200 mg (61.5% yield) of the amine (P-6). Analytical data for the amine (P-6): MS (CI, M+H) = 313, 315.

PREPARATION 7



- 33 -

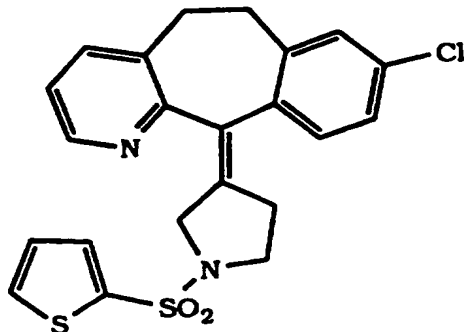


Combine 1.0 g (2.95 mmol) of E-isomer product (obtained using the appropriate ketone) from Preparation 3, Step E, 30 mL of glacial HOAc and 1.0 g (15.29 mmol) of Zn powder and heat the mixture at 100°C overnight. Filter through celite®, wash the filter cake with 20 mL of glacial HOAc, then concentrate the filtrate *in vacuo* to a residue. Basify the residue with 15 mL of concentrated NH₄OH (aqueous), add 50 mL of water and extract with CH₂Cl₂ (2 X 100 mL). Dry the combined extracts over MgSO₄, filter and concentrate *in vacuo* to a residue. Chromatograph the residue (silica gel, 5% MeOH/EtOAc + 2% concentrated NH₄OH (aqueous)) to give three products: 300 mg (30% yield) of the product (a); 250 mg (25% yield) of the product (b); and 250 mg (25% yield) of the product (c).

Analytical data for product (c): m.p. = 172°-173°C, MS (Cl, M+H) = 341, 343.

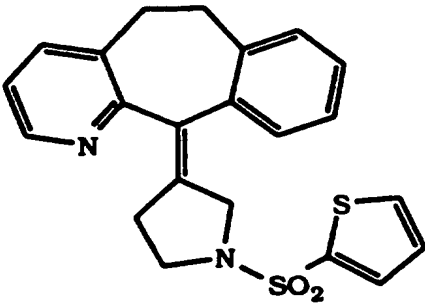
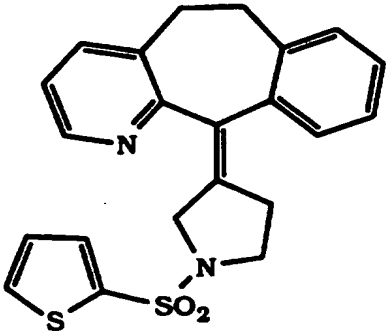
Analytical data for product (b): m.p. = 142°-144°C, MS (Cl, M+H) = 339, 341.

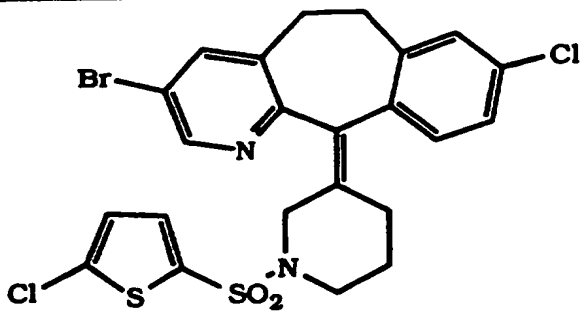
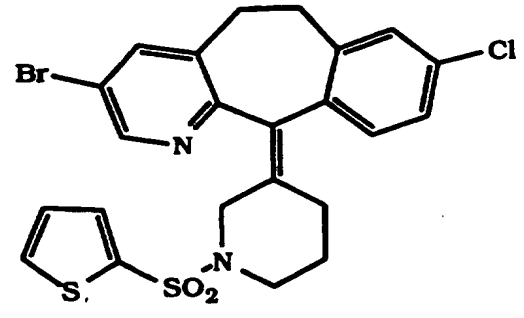
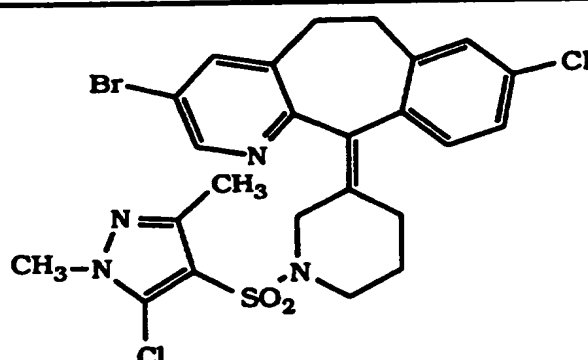
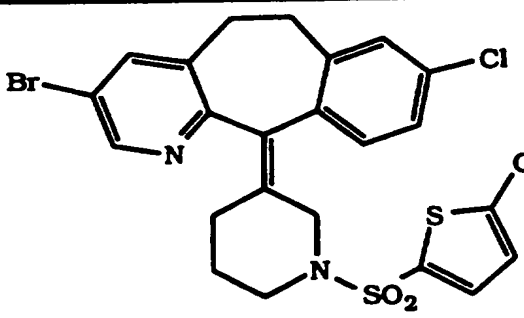
EXAMPLE 1

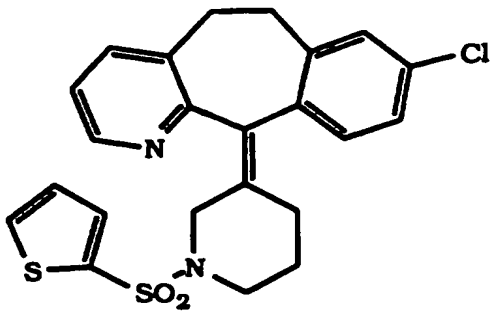
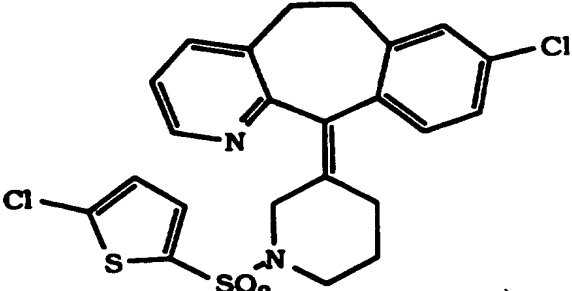
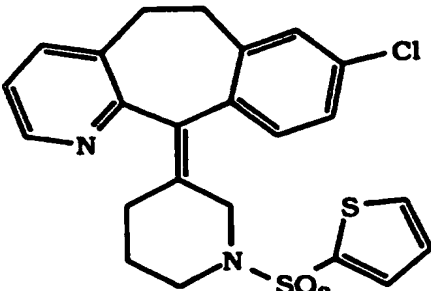
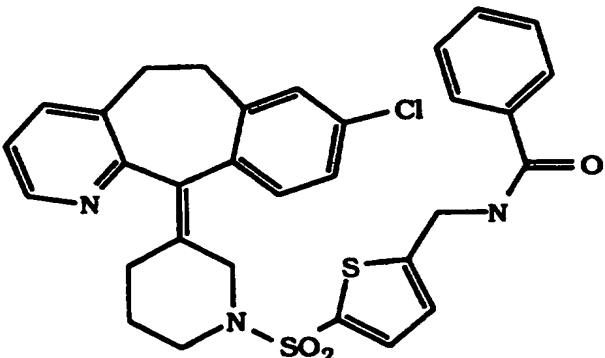


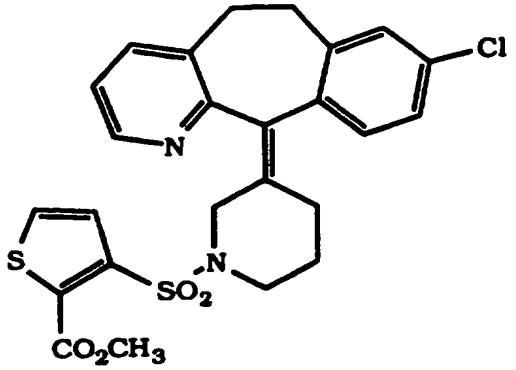
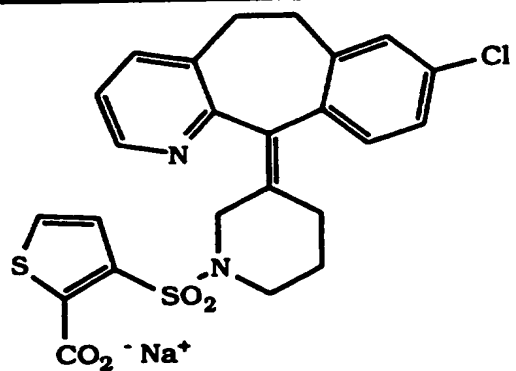
Combine 115 mg of the Z-amine product (P-1) from Preparation 1 (0.389 mmol), 5 mL of pyridine (5 mL) and a catalytic amount (15 mg) of DMAP under a N₂ atmosphere. Cool the solution to 0°C and add 175 mg of 2-thienylsulfonyl chloride (0.961 mmol). Stir for 10 min. at 0°C, then warm to room temperature and stir for 17 hours. Quench the reaction mixture by the adding a solution of NaHCO₃ (aqueous), and extract the aqueous layer with EtOAc-THF (20:1). Combine the extracts, wash with brine, dry over Na₂SO₄, filter and concentrate *in vacuo* to a residue. Chromatograph (silica gel, 25% EtOAc:hexane increasing gradually to 35% EtOAc:hexane) to give 65 mg (39% yield) of the Z-N-(2-thienyl)sulfonamide product (E-1). Analytical data for the Z-N-(2-thienyl)sulfonamide: MS (CI, M+H) = 443.

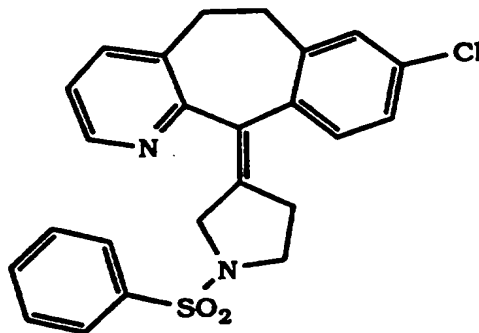
Using the appropriate sulfonyl chloride and the amine indicated, and following substantially the same procedure as described for Example 1, the following sulfonamide compounds were prepared:

Amine	Amide	Analytical Data
P-2A	 <p>(E-1A)</p>	MS (FAB, M+H) = 443
P-1A	 <p>(E-1B)</p>	MS (CI, M+H) = 409

P-3	 <p>(E-1C)</p>	m.p. = 165°-167°C MS (CI, M+H) = 569, 571
P-3	 <p>(E-1D)</p>	m.p. = 183°-184°C MS (CI, M+H) = 535, 537
P-3	 <p>(E-1E)</p>	m.p. = 251°-252°C MS (CI) = 583, 585
P-4	 <p>(E-1F)</p>	m.p. = 171°-172°C MS (CI) 569, 571

P-3A	 (E-1G)	MS (Cl, M+H) = 457, 459
P-3A	 (E-1H)	m.p. = 154°- 155°C MS (Cl) = 452, 454
P-4A	 (E-1J)	m.p. = 254- 255°C MS (Cl, M+H) = 457, 459
P-4A	 (E-1K)	MS (Cl, M+H) = 590, 592

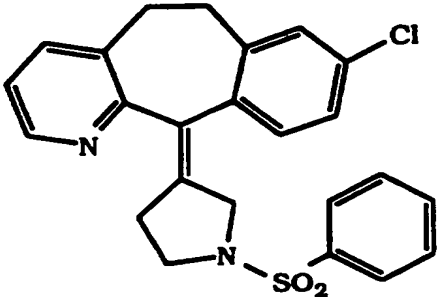
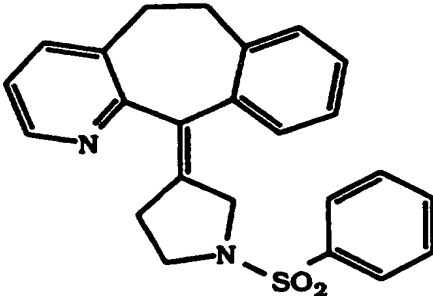
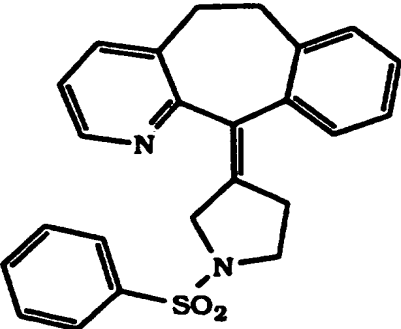
P-3A	 <p>(E-1M)</p>	<p>m.p. = 134°-136°C MS (CI, M+H) = 515, 517</p>
P-3A	 <p>(E-1N)</p>	<p>m.p. = 220°C (dec.) MS (FAB, M+H) = 501, 503</p>

EXAMPLE 2

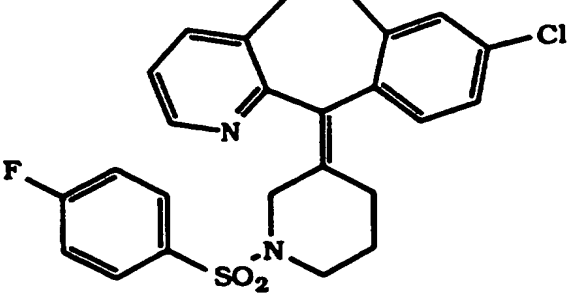
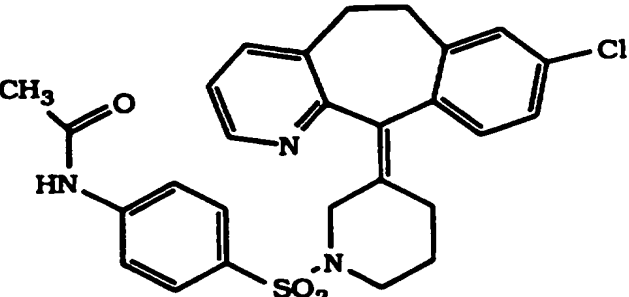
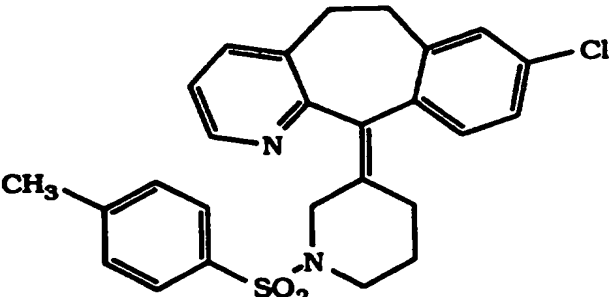
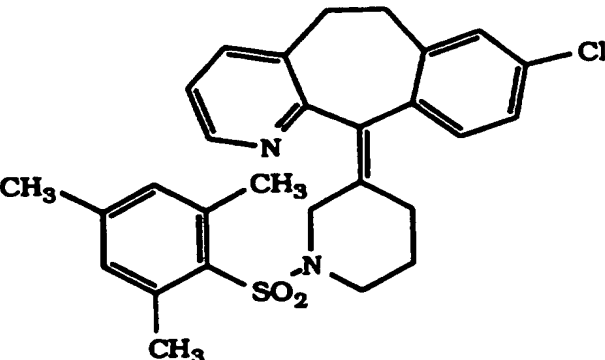
- Combine 110 mg of the Z-amine product (P-1) from Preparation 1 (0.339 mmol), 5 mL of pyridine and a catalytic amount (10 mg) of DMAP under a N₂ atmosphere. Cool the solution to 0°C and add C₆H₅SO₂Cl (1.17 mmol, 207 mg). Stir the mixture for 10 min at 0°C, then warm to room temperature and stir for 17h. Add a solution of NaHCO₃ (aqueous) to quench the reaction mixture, then extract the aqueous layer with EtOAc-THF (20:1). Combine the extracts, wash with brine, dry over Na₂SO₄, filter and concentrate *in vacuo* to a residue. Chromatograph

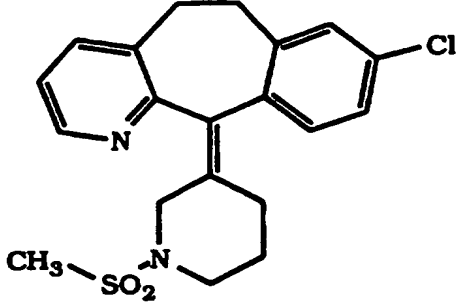
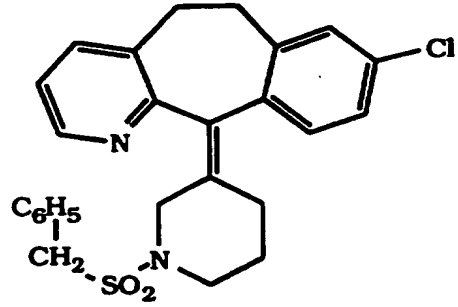
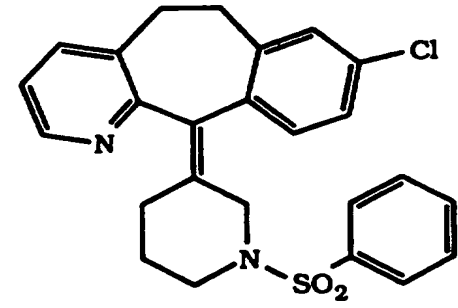
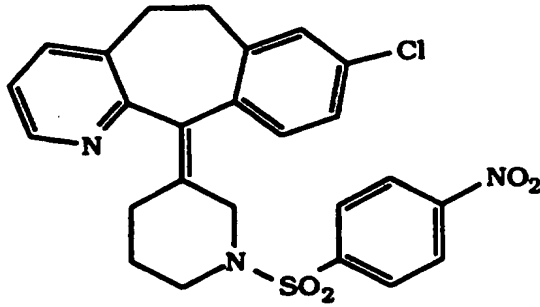
(silica gel, 25% EtOAc:hexane increasing gradually to 35% EtOAc:hexane) to give 80 mg (54 % yield) of the Z-benzene-sulfonamide product (E-2). Analytical data for the Z-N-benzenesulfonamide: MS (CI, M+H) = 437.

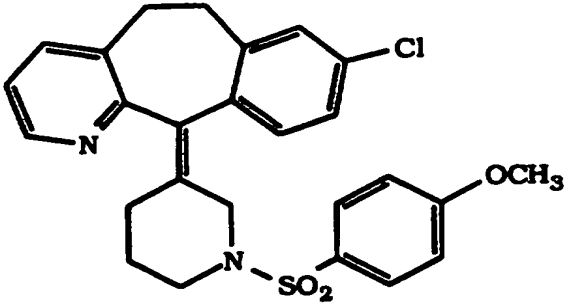
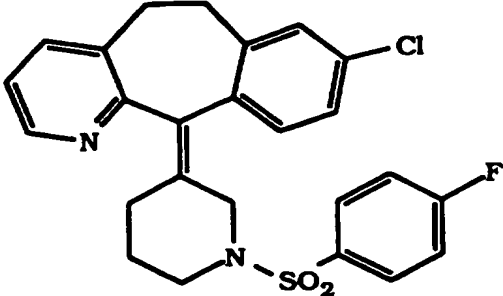
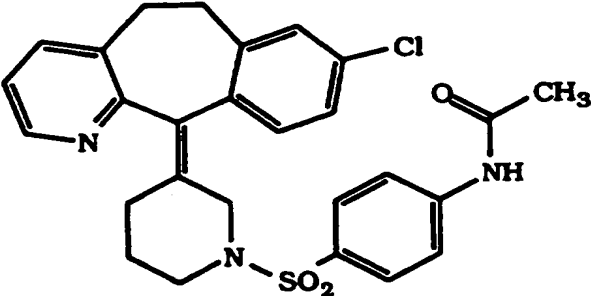
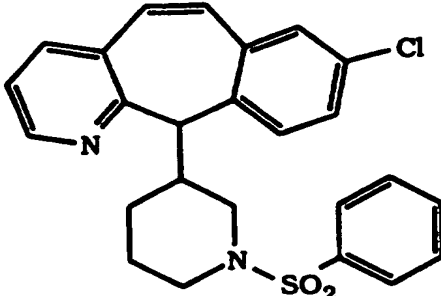
- 5 Using the appropriate sulfonyl chloride and the amine indicated, and following substantially the same procedure as described for Example 2, the following sulfonamide compounds were prepared:

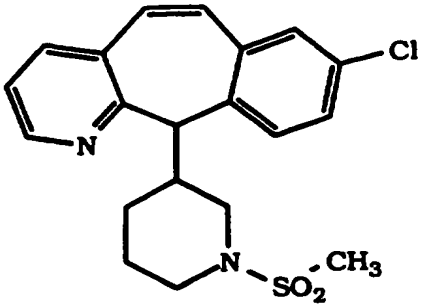
Amine	Amide	Analytical Data
P-2	 (E-2A)	MS (FAB, M+H) = 437
P-2A	 (E-2B)	
P-1A	 (E-2C)	MS (CI, M+H) = 403

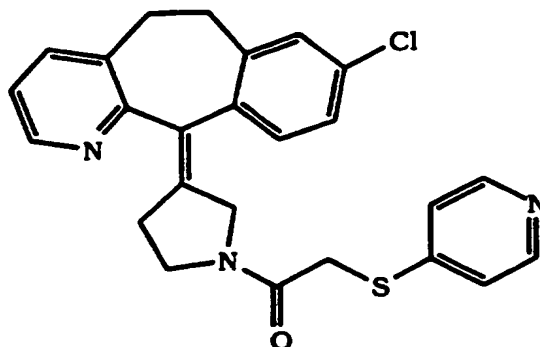
P-3	<p>(E-2D)</p>	m.p. = 184°- 185°C MS (CI, M+H) = 529, 531
P-3A	<p>(E-2E)</p>	MS (CI) = 451, 453
P-3A	<p>(E-2F)</p>	m.p. = 178°- 179°C MS (CI, M+H) = 496
P-3A	<p>(E-2G)</p>	m.p. = 160°- 161°C MS (CI) = 481, 483

P-3A	 (E-2H)	m.p. = 173°- 174°C MS (CI, M+H) = 469, 471
P-3A	 (E-2J)	m.p. = 162°- 163°C MS (CI) = 508, 510
P-3A	 (E-2K)	MS (CI) = 465, 467
P-3A	 (E-2L)	m.p. = 227°- 229°C MS (CI) = 493, 495

P-3A	 <p>(E-2M)</p>	m.p. = 189°- 190°C MS (CI, MH) = 389, 391
P-3A	 <p>(E-2N)</p>	m.p. = 198°- 199°C MS (CI) = 465, 467
P-4A	 <p>(E-2P)</p>	m.p. = 235°- 236°C MS (CI, M+H) = 451, 453
P-4A	 <p>(E-2Q)</p>	m.p. = 232°- 233°C MS (CI, M+H) = 496, 498

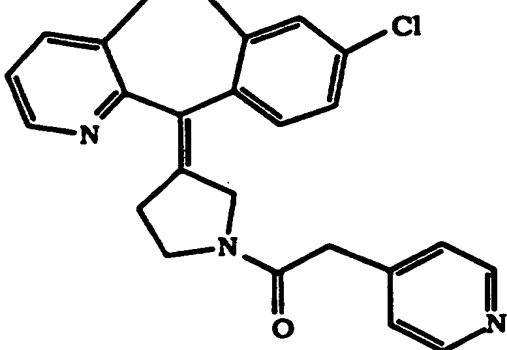
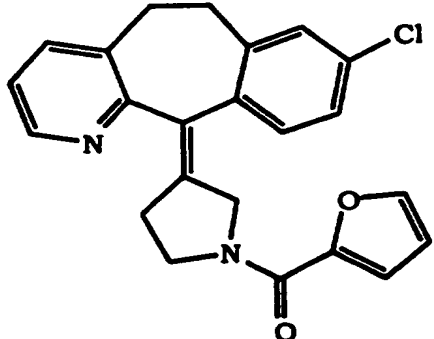
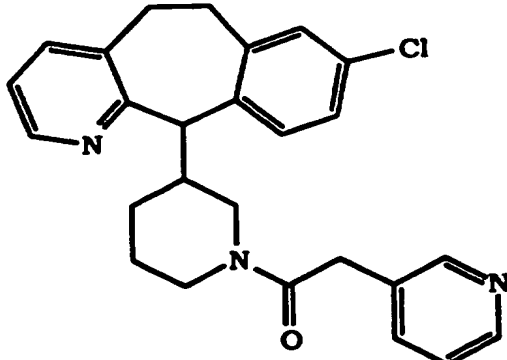
P-4A	 <p>(E-2R)</p>	m.p. = 168°- 169°C MS (CI, M+H) = 481, 483
P-4A	 <p>(E-2S)</p>	m.p. = 154°- 155°C MS (CI, M+H) = 469, 471
P-4A	 <p>(E-2T)</p>	m.p. = 147°- 149°C MS (CI, M+H) = 508, 510
P-5	 <p>(E-2U)</p>	m.p. = 178°- 179°C MS (FAB, M+H) = 451, 453

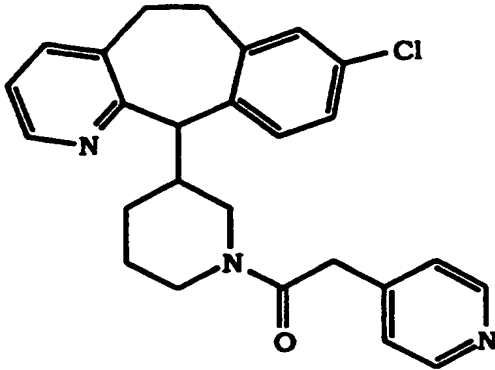
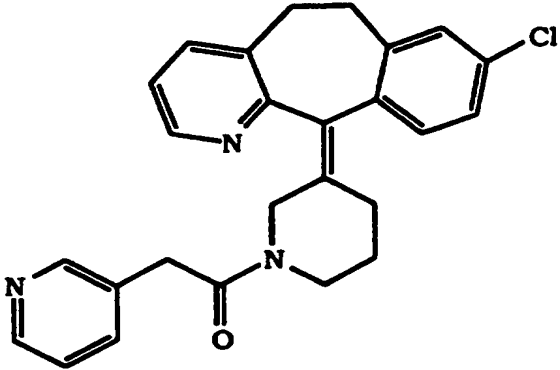
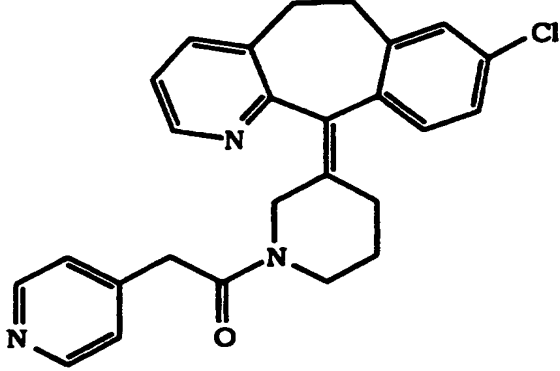
P-5	 <p>(E-2V)</p>	<p>M.P. = 231°-232°C MS (CI, M+H) = 389, 391</p>
-----	---	--

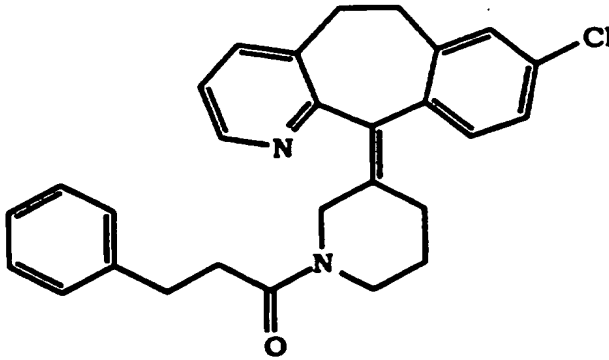
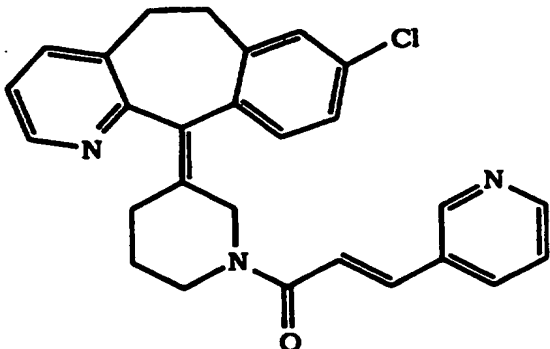
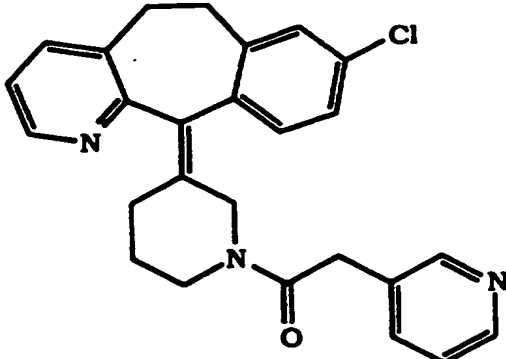
EXAMPLE 3

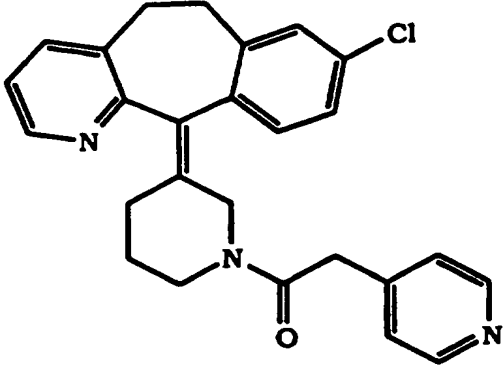
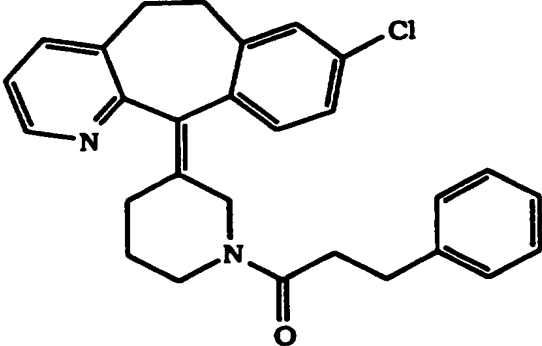
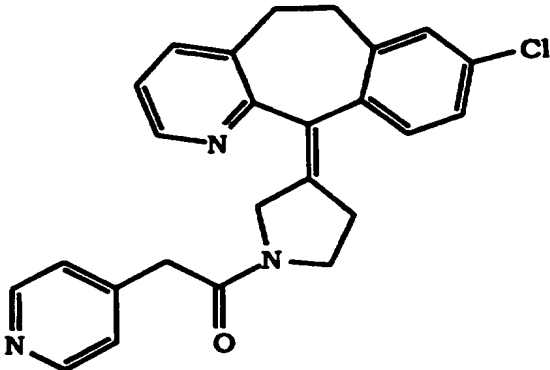
Combine 80 mg of the E-amine product (P-2) from Preparation 2 (0.270 mmol) 3 mL of DMF and 2 mL of NMM under a N₂ atmosphere. Cool the mixture to 0°C and add 110 mg of HOBT (0.888 mmol), 250 mg of DEC (1.31 mmol), and 0.651 mmol of (4-pyridylthio)acetic acid. After 30 min., warm to room temperature and stir for 24 hours. Concentrate *in vacuo* to a residue, dilute the residue with NaHCO₃ (aqueous), and extract with CH₂Cl₂. Combine the extracts, wash with brine, dry over Na₂SO₄, filter and concentrate *in vacuo* to give a residue. Decolorize with activated carbon and chromatograph (silica gel, 5% MeOH:CH₂Cl₂ increasing gradually to 10% MeOH:CH₂Cl₂) to give 45 mg (37% yield) of the E-(4-pyridylthio)amide product (E-3). Analytical data for the E-(4-pyridylthio)amide: MS (CI, M+H) = 448.

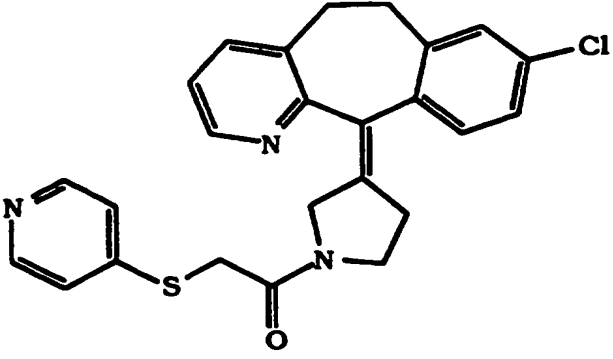
Using the appropriate carbocyclic acid and the amine indicated, and following substantially the same procedure as described for Example 3, the following amide compounds were prepared:

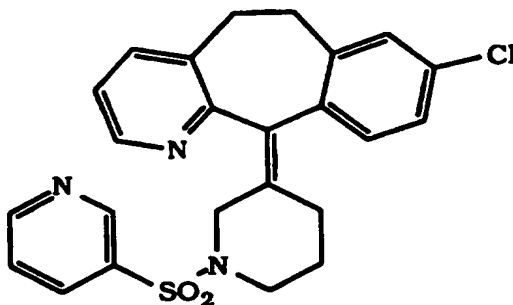
Amin	Amid	Analytical Data
P-2	 (E-3A)	MS (Cl, M+H) = 415
P-2	 (E-3B)	MS (Cl, M+H) = 391
P-6	 (E-3C)	MS (Cl, M+H) = 432, 434

P-6	 <p>(E-3D)</p>	MS (Cl, M+H) = 432, 434
P-3A	 <p>(E-3E)</p>	MS (Cl, M+H) = 430, 432
P-3A	 <p>(E-3F)</p>	MS (Cl, M+H) = 430, 432

P-3A	 (E-3G)	MS (Cl, M+H) = 443, 445
P-4A	 (E-3H)	m.p. = 165°- 166°C MS (Cl, M+H) = 442, 444
P-4A	 (E-3J)	m.p. = 157°- 158°C MS (Cl, M+H) = 430, 432

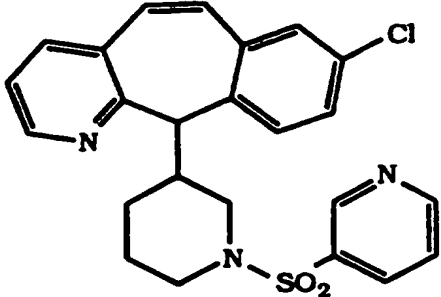
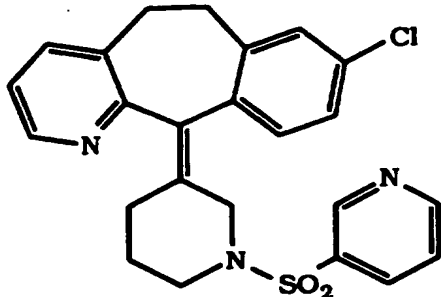
P-4A	 <p>(E-3K)</p>	MS (Cl, M+H) = 430, 432
P-4A	 <p>(E-3L)</p>	MS (Cl, M+H) = 443, 445
P-1	 <p>(E-3M)</p>	MS (Cl, M+H) = 416

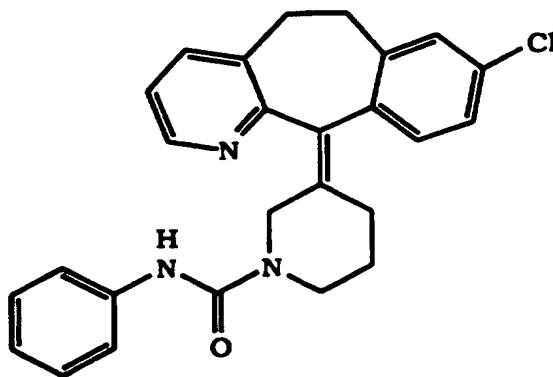
P-1	 <p>(E-3N)</p>	MS (CI, M+H) = 448
-----	--	-----------------------

EXAMPLE 4

- Combine 100 mg (0.626 mmol) of 3-pyridinesulfonic acid and 3 mL of anhydrous pyridine at 0°C and add 100mg (0.406 mmol) of 4-nitrobenzenesulfonyl chloride. Add 5 mg of DMAP and stir the mixture at 0°C for 7 hours. Add 80 mg (0.258 mmol) of the Z-amine (P-3A) from Preparation 3 and stir the mixture for 1 hour at 0°C, then overnight at 20°C. Add 50 mL of CH₂Cl₂ and 20 mL of water, separate the layers, and wash the organic phase with water. Dry over MgSO₄, filter and concentrate *in vacuo* to a residue. Chromatograph the residue (silica gel, 5% MeOH/EtOAc + 1% concentrated NH₄OH (aqueous)), crystallize from 10 mL of Et₂O and dry the resulting solid at 60°C *in vacuo* to give 180 mg (68.9% yield) of the Z-3-pyridylsulfonamide product (E-4).
- Analytical data for the Z-3-pyridylsulfonamide (E-4): m.p. = 158°-159°C; MS (CI) = 452, 454.

Using the the E- or Z-amine indicated, and following substantially the same procedure as described for Example 4, the following sulfonamide compounds were prepared:

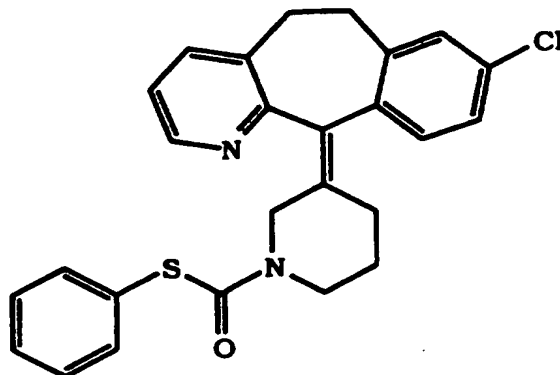
Amin	Amide	Analytical Data
P-5	 <p>(E-4A)</p>	m.p. = 178°-179°C MS (CI, M+H) = 452, 454
P-4A	 <p>(E-4B)</p>	m.p. = 214°-215°C MS (CI, M+H) = 452, 454

EXAMPLE 5

- Combine 70 mg (0.225 mmol) of Z-amine (P-3A) from Preparation 3, 0.2 mL (1.53 mmol) of $C_6H_5N=C=O$ and 15 mL of CH_2Cl_2 at 0°C, add 0.2 mL (2.72 mmol) of Et_3N and stir at 20°C overnight. Add 20 mL of water and 25 mL of CH_2Cl_2 , separate the layers and dry the organic phase over $MgSO_4$. Filter, concentrate *in vacuo* to a residue, chromatograph the residue (silica gel, 20% EtOAc/hexanes) and crystallize from 10 mL of Et_2O . Dry the resulting solid *in vacuo* at 20°C to give 75 mg (78% yield) of the

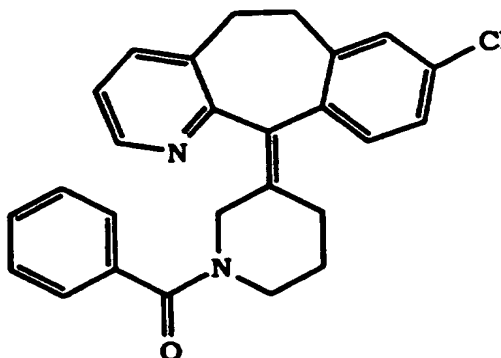
Z-phenylurea product (E-5). Analytical data for the Z-phenylurea (E-5): m.p. = 184°-185°C; MS (CI, M+H) = 430, 432.

EXAMPLE 6



- 5 Combine 25 mg (0.08 mmol) of the Z-amine (P-3A) from Preparation 3, 0.2 mL (2.72 mmol) of Et₃N and 2 mL of anhydrous pyridine at 0°C and add 0.2 g (1.13 mmol) of phenyl chlorothioformate. Add 5 mg (0.04 mmol) of DMAP and stir the mixture overnight. Concentrate *in vacuo* to a residue and partition the residue between 25 mL of EtOAc and 20 mL of water. Dry the organic phase over Na₂SO₄, filter and concentrate *in vacuo* to a residue. Chromatograph the residue (silica gel, 5% MeOH/EtOAc), triturate with hexanes and dry the resulting solid at 20°C *in vacuo* to give 30 mg (83.6% yield) of the Z-phenylthiocarbamate product (E-6). Analytical data for the Z-phenylthiocarbamate (E-6): m.p. = 187°-188°C; MS (CI) = 447.
- 10
- 15

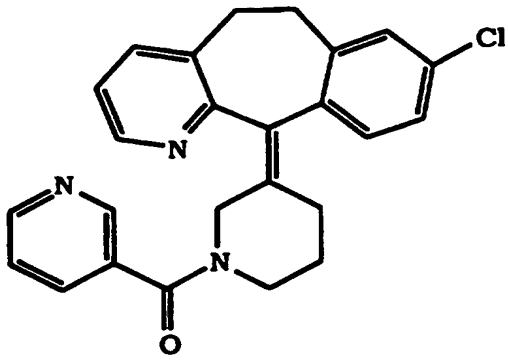
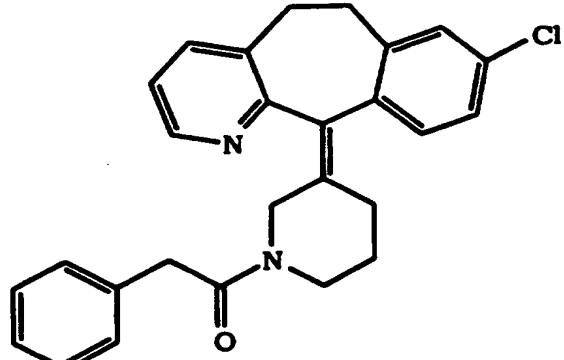
EXAMPLE 7



- 20 Combine 40 mg (0.129 mmol) of the Z-amine (P-3A) from Preparation 3, 0.5 mL (0.391 mmol) of benzoyl chloride and 5 mL of anhydrous pyridine at 0°C, add 2 mg of DMAP, then stir the mixture overnight at 20°C. Add 20 mL of CH₂Cl₂ and 10 mL of water, separate the layers and wash the organic phase with 20 mL

- of brine. Dry the organic phase over MgSO_4 , filter and concentrate *in vacuo* to a residue. Chromatograph the residue (silica gel, 5% MeOH/EtOAc + 1% concentrated NH_4OH (aqueous)), recrystallize the resulting solid from acetone/hexanes and dry the at 60°C *in vacuo* to give the Z-phenylamide product (E-7). Analytical data for the Z-phenylamide (E-7): m.p. = $215^\circ\text{--}216^\circ\text{C}$; MS (CI, M+H) = 415, 417.

- Using the appropriate acid chloride and the E- or Z-amine indicated, and following substantially the same procedure as described for Example 7, the following amide compounds were prepared:

Amine	Amide	Analytical Data
P-3A	 <p>(E-7A)</p>	MS (CI, M+H) = 416, 418
P-3A	 <p>(E-7B)</p>	MS (CI, M+H) = 429, 431

ASSAYS

- FPT IC_{50} (inhibition of farnesyl protein transferase, *in vitro* enzyme assay), GGPT IC_{50} (inhibition of geranylgeranyl protein transferase, *in vitro* enzyme assay), COS Cell IC_{50} (Cell-Based Assay) and Cell Mat Assay were determined following the assay procedures in WO 95/10516.

TABLE 2 - FPT INHIBITION

COMPOUND	FPT IC ₅₀ (μM)	COS IC ₅₀ (μM)
E-1	0.01-10	-----
E-1A	-----	-----
E-1B	0.01-10	-----
E-2	0.01-10	0.01-10
E-2A	-----	-----
E-2B	-----	-----
E-2C	0.01-10	-----
E-3	0.01-10	-----
E-3A	10-100	-----
E-3B	10-100	-----
E-3C	0.01-10	-----
E-3D	10-100	-----
E-3J	0.01-10	-----
E-3K	10-100	-----
E-3L	10-100	-----
E-3H	-----	-----
E-2P	0.01-10	-----
E-4B	0.01-10	-----
E-2Q	10-100	-----
E-1J	0.01-10	-----
E-2R	10-100	-----
E-2T	10-100	-----
E-2S	10-100	-----
E-1K	10-100	-----
E-3E	10-100	-----
E-3F	10-100	-----
E-7A	10-100	-----
E-7B	10-100	-----
E-6	10-100	-----
E-2E	0.01-10	0.01-10
E-3G	10-100	-----
E-2M	10-100	-----
E-7	>100	-----
E-1G	0.01-10	-----

E-2J	10-100	-----
E-2H	10-100	-----
E-2G	10-100	-----
E-2F	10-100	-----
E-4	0.01-10	-----
E-1H	0.01-10	-----
E-2K	10-100	-----
E-2L	10-100	-----
E-2N	10-100	-----
E-5	10-100	-----
E-1D	0.01-10	-----
E-2D	0.01-10	-----
E-2U	0.01-10	-----
E-2V	10-100	-----
E-4A	0.01-10	-----
E-3N	0.01-10	-----
E-3M	10-100	-----

TABLE 2**COMPARISON OF FPT INHIBITION AND GGPT INHIBITION**

COMPOUND	ENZYME INHIBITION FPT IC ₅₀ μ M	ENZYME INHIBITION GGPT IC ₅₀ μ M
E-2E	0.01-10	7.4 mM
E-1G	0.01-10	<13

TABLE 3**INHIBITION OF TUMOR CELL GROWTH - MAT ASSAY**

COMPOUND	INHIBITION OF TUMOR CELL GROWTH (IC ₅₀ μ M)	INHIBITION OF NORMAL CELL GROWTH (IC ₅₀ μ M)
E-2E	<3.1	>50
E-1G	12.5	>25
E-2H	12.5	>25

RESULTS

1. Enzymology:

The data demonstrate that the compounds of the invention are inhibitors of Ras-CVLS farnesylation by partially purified rat and human brain farnesyl protein transferase (FPT). The data also show that there are compounds of the invention which can be considered as potent ($IC_{50} < 10 \mu M$) inhibitors of Ras-CVLS farnesylation by partially purified rat brain farnesyl protein transferase (FPT)--see Table 2.

The data also demonstrate that compounds of the invention are poorer inhibitors of geranylgeranyl protein transferase (GGPT) assayed using Ras-CVLL as isoprenoid acceptor. Tested compounds were inactive or weakly active as geranylgeranyl transferase inhibitors at $20 \mu g/ml$. This selectivity is important for the therapeutic potential of the compounds used in the methods of this invention, and increases the potential that the compounds will have selective growth inhibitory properties against Ras-transformed cells.

2. Cell-Based: COS Cell and Cell Mat Assays

Immunoblot analysis of the Ras protein expressed in Ras-transfected COS cells indicated that the farnesyl transferase inhibitors of this invention inhibit Ras-CVLS processing, causing accumulation of unprocessed Ras (Table 2). For example, compounds E-2 and E-2E inhibit Ras-CVLS processing with IC_{50} values of >5 and $2.5 \mu M$, respectively. These results show that the compounds inhibit farnesyl protein transferase in intact cells and indicate their potential to block cellular transformation by activated Ras oncogenes.

Compounds of this invention also inhibited the growth of Ras-transformed tumor cells in the Mat assay. For example, compound E-2E inhibited with an IC_{50} value of $<3.1 \mu M$. This compound only displayed cytotoxic activity against the normal cell monolayer at higher concentrations (IC_{50} of $>50 \mu M$).

In Vivo Anti-Tumor Studies:

The anti-tumor activity of compounds of the present invention can also be determined by the method described in WO 95/10516.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 70 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar, lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection.

Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 0.1 mg to 1000 mg, more preferably from about 1 mg. to 300 mg, according to the particular application.

5 The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum
10 dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

15 The amount and frequency of administration of the compounds of the invention and the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being
20 treated. A typical recommended dosage regimen is oral administration of from 10 mg to 2000 mg/day preferably 10 to 1000 mg/day, in two to four divided doses to block tumor growth. The compounds are non-toxic when administered within this dosage range.

25 The following are examples of pharmaceutical dosage forms which contain a compound of the invention. The scope of the invention in its pharmaceutical composition aspect is not to be limited by the examples provided.

Pharmaceutical Dosage Form ExamplesEXAMPLE A - Tablets

No.	Ingredients	mg/tablet	mg/tablet
1.	Active compound	100	500
2.	Lactose USP	122	113
3.	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	40
4.	Corn Starch, Food Grade	45	40
5.	Magnesium Stearate	3	7
Total		300	700

Method of Manufacture

- Mix Item Nos. 1 and 2 in a suitable mixer for 10-15 minutes. Granulate the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., 1/4", 0.63 cm) if necessary. Dry the damp granules. Screen the dried granules if necessary and mix with Item No. 4 and mix for 10-15 minutes. Add Item No. 5 and mix for 1-3 minutes. Compress the mixture to appropriate size and weigh on a suitable tablet machine.

10

EXAMPLE B - Capsules

No.	Ingredient	mg/capsule	mg/capsule
1.	Active compound	100	500
2.	Lactose USP	106	123
3.	Corn Starch, Food Grade	40	70
4.	Magnesium Stearate NF	7	7
Total		253	700

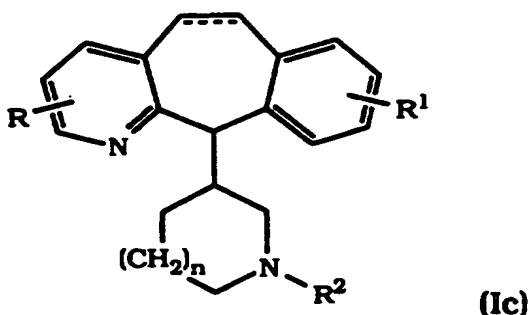
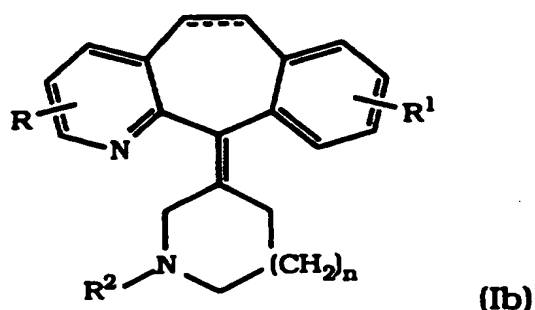
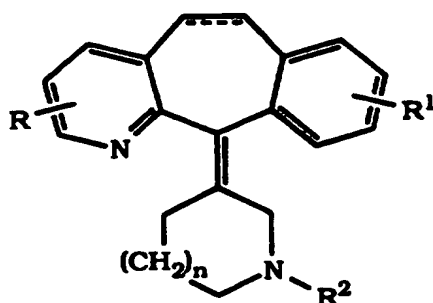
Method of Manufacture

- Mix Item Nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add Item No. 4 and mix for 1-3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

- While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

WHAT IS CLAIMED IS:

1. A method for inhibiting the abnormal growth of cells comprising administering an effective amount of a compound of formula (Ia), (Ib) or (Ic)



wherein:

- R and R¹ are independently selected from H, (C₁-C₆)alkyl, halogeno, OH, (C₁-C₆)alkoxy; NH₂; (C₁-C₆)alkylamino; di((C₁-C₆)alkyl)amino; CF₃; SO₃H; CO₂R³; NO₂; SO₂NH₂; and CONHR⁴;
- R² is R⁵C(O)-, R⁵CH₂C(O)-, R⁵C(R⁶)₂C(O)-, R⁵SO₂-, R⁵CH₂SO₂-, R⁵SCH₂C(O)-, R⁵OC(O)-, R⁵NHC(O)-, R⁵C(O)C(O)- or R⁵SC(O)-;
- R³ is (C₁-C₆)alkyl, aryl;
- R⁴ is (C₁-C₆)alkyl;
- R⁵ is (C₁-C₆)alkyl, aryl, aryl(C₁-C₆)alkyl, aryl(C₂-C₆)alkenyl, heteroaryl, heteroaryl(C₁-C₆)alkyl, heteroaryl(C₂-C₆)alkenyl or heterocycloalkyl;
- each R⁶ independently represents (C₁-C₆)alkyl, or both R⁴ groups together with the carbon atom to which they are attached comprise a (C₃-C₇)carbocyclic ring;
- n is 0 or 1; and
- the dotted line represents an optional double bond;
- and pharmaceutically acceptable salts thereof.

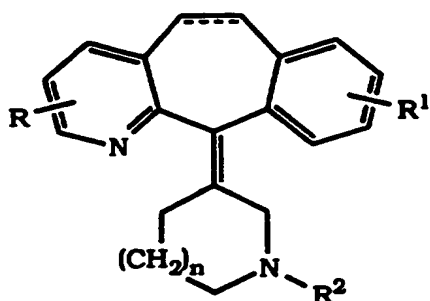
2. The method of Claim 1 wherein the cells inhibited are tumor cells expressing an activated Ras oncogene.

3. The method of Claim 2 wherein the cells inhibited are
5 pancreatic tumor cells, lung cancer tumor cells, epidermal carcinoma tumor cells, myeloid leukemia tumor cells, thyroid follicular tumor cells, myelodysplastic cells, bladder carcinoma tumor cells or colon tumor cells.

10 4. The method of Claim 1 wherein the inhibition of the abnormal growth of cells occurs by the inhibition of farnesyl protein transferase.

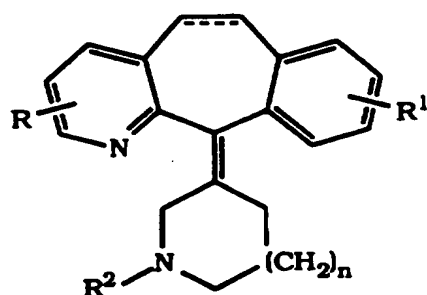
5. The method of Claim 1 wherein the inhibition is of
15 tumor cells wherein Ras protein is activated as a result of oncogenic mutation in genes other than the Ras gene.

6. A compound selected from a compound of the formula (Ia), (Ib) or (Ic)

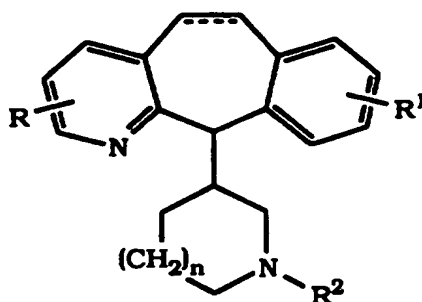


20

(Ia) ,



(Ib)



(Ic)

wherein:

R and R¹ are independently selected from H, (C₁-C₆)alkyl, halogeno, OH, (C₁-C₆)alkoxy, NH₂, (C₁-C₆)alkylamino, di((C₁-
25 C₆)alkyl)amino, CF₃, SO₃H, CO₂R³, NO₂, SO₂NH₂, and CONHR⁴;

R^2 is $R^5C(O)-$, $R^5CH_2C(O)-$, $R^5C(R^6)_2C(O)-$, R^5SO_2- , $R^5CH_2SO_2-$, $R^5SCH_2C(O)-$, $R^5OC(O)-$, $R^5NHC(O)-$, $R^5C(O)C(O)-$ or $R^5SC(O)-$;

R^3 is (C_1-C_6) alkyl, aryl;

5 R^4 is (C_1-C_6) alkyl;

R^5 is (C_1-C_6) alkyl, aryl, aryl (C_1-C_6) alkyl, aryl (C_2-C_6) alkenyl, heteroaryl, heteroaryl (C_1-C_6) alkyl, heteroaryl (C_2-C_6) alkenyl or heterocycloalkyl;

10 each R^6 independently represents (C_1-C_6) alkyl, or both R^6 groups together with the carbon atom to which they are attached comprise a (C_3-C_7) carbocyclic ring;

n is 0 or 1; and

the dotted line represents an optional double bond;
and pharmaceutically acceptable salts thereof.

15

7. A compound of claim 6 having the structure (Ib).

8. A compound of claim 6 wherein R and R^1 are independently selected from H or halogeno.

20

9. A compound of claim 8 wherein R^2 is $R^5C(O)-$, $R^5CH_2C(O)-$, $R^5SCH_2C(O)-$, R^5SO_2- , $R^5CH_2SO_2-$, $R^5NHC(O)-$ or $R^5SC(O)-$;

25

10. A compound of claim 9 wherein R^5 is methyl, phenyl, benzyl, 2-thienyl, 4-pyridyl, 3-pyridyl, 5-chloro-2-thienyl, p-tolyl, p-nitrophenyl, p-fluorophenyl, p-acetoxyphenyl, 5-chloro-1,3-dimethyl-4-pyrazolyl, 2,4,6-trimethylphenyl, 5-(benzoylamino-methyl)-2-thienyl, 2-methoxycarbonyl-3-thienyl, 4-pyridylthio, 2-furanyl, E-(3-pyridyl)ethenyl, p-methoxyphenyl, p-acetamidophenyl, or the sodium salt of 2-carboxy-3-thienyl.

30

11. A compound of claim 7 wherein R^2 is $R^5C(O)-$, and R^5 is 2-furanyl or E-(3-pyridyl)ethenyl.

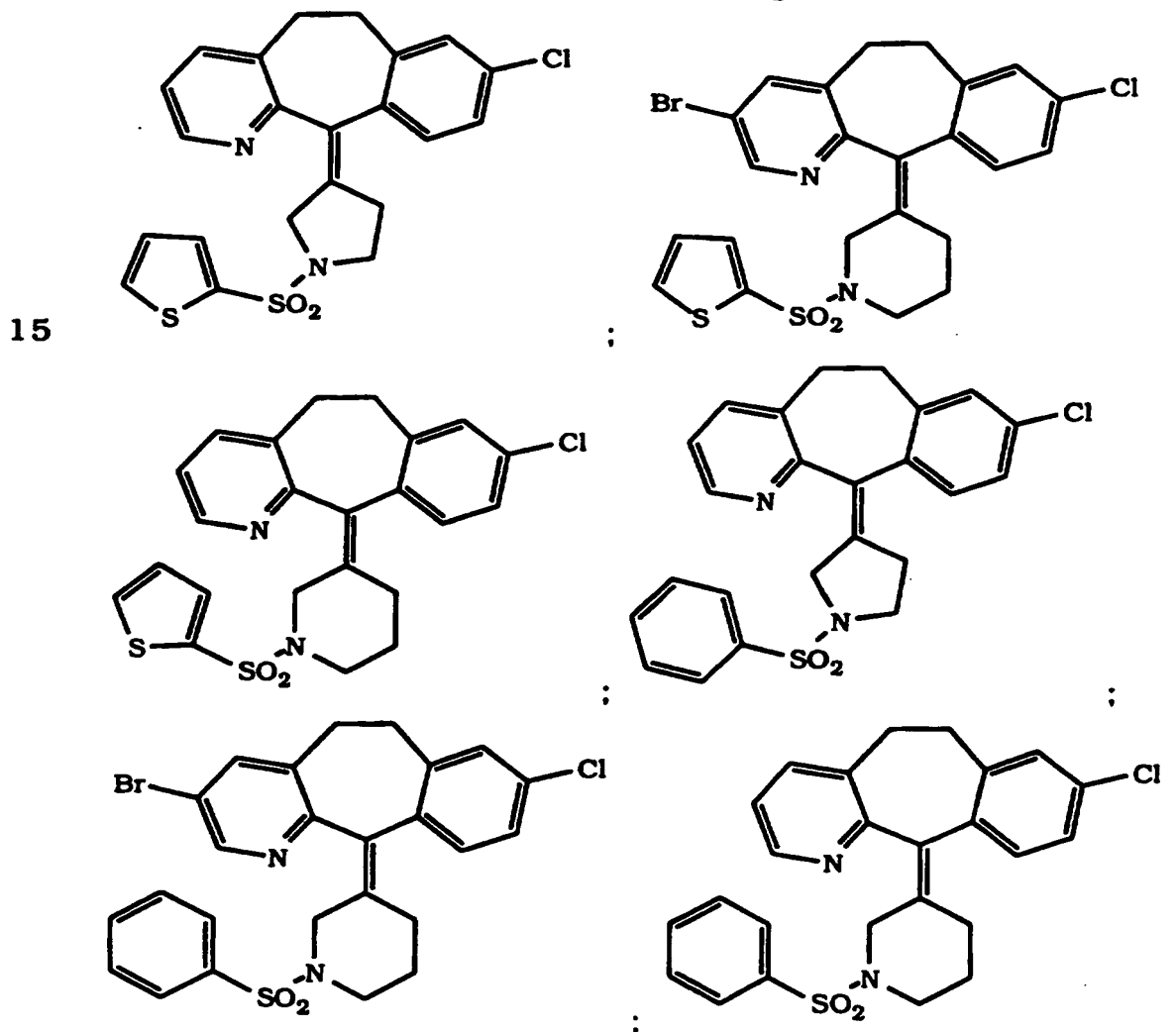
35

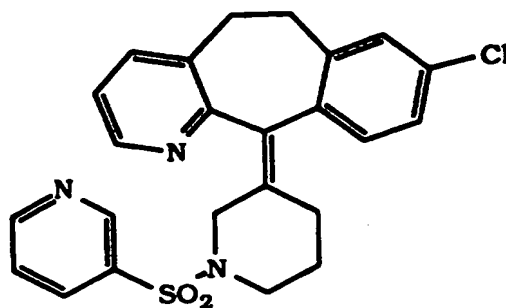
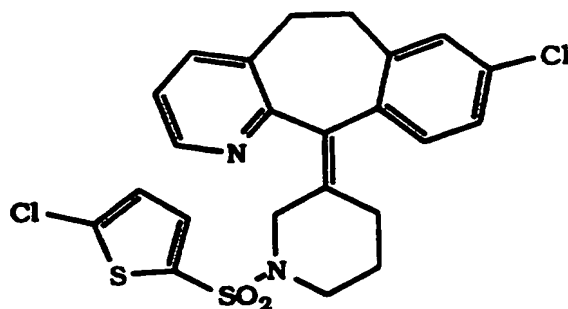
12. A compound of claim 7 wherein R^2 is $R^5CH_2C(O)-$, and R^5 is 4-pyridylthio, 4-pyridyl, 3-pyridyl or benzyl.

13. A compound of claim 7 wherein R^2 is R^5SO_2- , and R^5 is 2-thienyl, 5-chloro-2-thienyl, 5-chloro-1,3-dimethyl-4-pyrazolyl, 5-(benzoylaminomethyl)-2-thienyl, 2-methoxycarbonyl-3-thienyl, phenyl, p-nitrophenyl, p-methoxyphenyl, p-fluorophenyl, p-acetamidophenyl, p-tolyl, 2,4,6-trimethylphenyl, methyl, benzyl, 3-pyridyl or the sodium salt of 2-carboxy-3-thienyl.

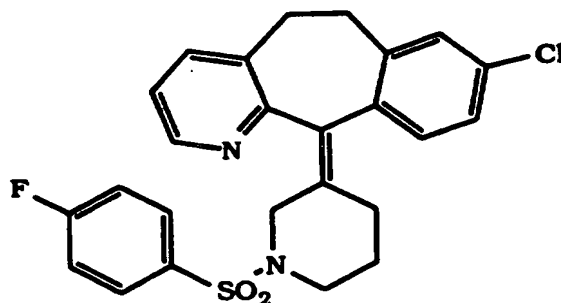
14. A compound of claim 7 wherein R^2 is selected from $R^5CH_2SO_2-$ wherein R^5 is phenyl; $R^5NHC(O)-$ wherein R^5 is phenyl; $R^5SC(O)-$, wherein R^5 is phenyl; R^5SO_2- wherein R^5 is aryl or heteroaryl; or $R^5SCH_2C(O)-$ wherein R^5 is heteroaryl.

15. A compound of claim 7 having the structural formula





or



5

16. A pharmaceutical composition, for use in inhibiting the growth of abnormal cells, comprising a pharmaceutically acceptable carrier and an effective amount of a compound of Claim 6.

10

17. The use of a compound of Claim 6 for the manufacture of a medicament for use in inhibiting the abnormal growth of cells.

15

18. The use of a compound of Claim 6 for inhibiting the abnormal growth of cells.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US 96/03306A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/445 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	J.MED.CHEM., vol. 15, no. 7, 1972, pages 750-754, XP000578364 VILLANI ET AL.: "Derivatives of 10,11-dihydro-5H-dibenzo[a,d]cyclopentene and related compounds. 6. Aminoalkyl derivatives of the aza isosters" see table II, compound 52	1-18
A	WO,A,93 23400 (SCHERING) 25 November 1993 see page 15; example 1 see page 13 - page 14	1-18
A	WO,A,92 11034 (WELLCOME) cited in the application see claim 6	1-18

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search

20 August 1996

Date of mailing of the international search report

02.09.96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+ 31-70) 340-3016

Authorized officer

Gerli, P

INTERNATIONAL SEARCH REPORT

ion on patent family members

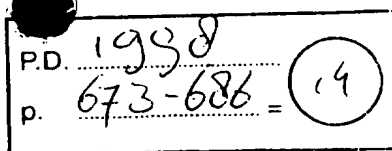
International Application No

PCT/US 96/03306

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9323400	25-11-93	AU-B- 4244593	13-12-93
WO-A-9211034	09-07-92	AT-T- 139447	15-07-96
		AU-B- 665341	04-01-96
		AU-B- 9062691	22-07-92
		CA-A- 2098198	18-06-92
		DE-D- 69120430	25-07-96
		EP-A- 0563134	06-10-93
		JP-T- 6504772	02-06-94
		US-A- 5416091	16-05-95



Pergamon



Bioorganic & Medicinal Chemistry 6 (1998) 673-686

 BIOORGANIC &
 MEDICINAL
 CHEMISTRY

Synthesis of Isomeric 3-Piperidinyl and 3-Pyrrolidinyl Benzo[5,6]cyclohepta[1,2-b]pyridines: Sulfonamido Derivatives as Inhibitors of Ras Prenylation

Joseph Kelly,^a Ronald Wolin,^a Michael Connolly,^a Adriano Afonso,^{a,*} Linda James,^a Paul Kirshmeier,^a W. Robert Bishop^a and Andrew T. McPhail^b

^aSchering-Plough Research Institute, 2015 Gallop Hill Road, Kenilworth, NJ 07033, USA

^bP. M. Gross Chemical Laboratory, Duke University, Durham, NC 27706, USA

Received 23 September 1997; accepted 17 November 1997

Abstract—Blocking farnesylation of oncogenic Ras proteins is a mechanism based therapeutic approach that is of current interest for the development of antitumor agents to treat *ras* associated tumors. As part of a SAR study on the lead farnesyl protein transferase (FPT) inhibitor I, we report here the synthesis of novel geometric isomers II and III and the FPT inhibition activity of their *N*-acyl and *N*-sulfonamido derivatives 15-65. The *N*-acyl derivatives are markedly less active than the lead inhibitor I thereby demonstrating that the spatial location of the *N*-acyl group in I is critical for binding of the compound to FPT. In contrast to I, the *N*-sulfonamido-II series is a novel lead of non-sulfhydryl, nonpeptidic compounds that are dual FPT/GGPT inhibitors. In light of recent reports on the alternative prenylation of N- and K-Ras, dual FPT/GGPT inhibitors may be required to control cell proliferation in tumors containing activated Ras. © 1998 Elsevier Science Ltd. All rights reserved.

Introduction

ras Oncogenes are present in a majority of human colon and pancreatic carcinomas.¹ The pathway by which Ras proteins regulate cell proliferation is now known; in this pathway, Ras proteins occupy a central role in a signal transduction cascade which is initiated by the binding of extra-cellular growth factors to their tyrosine kinase receptors, and ends in the nucleus with phosphorylation of key transcription factors that regulate gene expression.² The upstream signals in this cascade induce a guanine nucleotide exchange that converts the inactive GDP-bound Ras to its active GTP-bound state.³ Downstream signalling, and hence cell proliferation, proceeds until it is terminated by intrinsic GTPase activity of Ras which returns the active GTP-bound Ras to the inactive GDP-bound state.^{2,4} Oncogenic Ras is deficient in GTPase activity and this results in uncontrolled cell

proliferation.¹ Ras proteins are expressed in the cytosol and require a post-translational farnesylation on the cysteine residue of the carboxyl terminus CAAX tetrapeptide in order to acquire transforming ability; this prenylation step is catalyzed by the enzyme farnesyl protein transferase (FPT), and the farnesylated-Ras becomes functional by attachment to the inner plasma membrane.⁵ A majority of other cellular proteins are prenylated with a geranylgeranyl residue on the cysteine of their carboxyl-terminus sequence; these prenylations are catalyzed by Geranylgeranyl protein transferase (GGPT), an enzyme which is closely related to FPT.^{5,6} Selective inhibition of farnesylation of Ras by FPT has been an attractive therapeutic target for the development of antitumor agents to control tumorigenic cell proliferation in *ras* associated tumors.^{7,8} However, it is now known that N- and K-Ras can also undergo alternative prenylation.⁹⁻¹¹ Most of the potent FPT inhibitors reported in the literature to date are peptidomimetics or peptides based on the CAAX sequence and contain a free thiol group.¹² FPT inhibitors that are nonthiol peptides have also been reported.¹³ However, the peptidic nature or the presence of a free thiol group

Key words: FPT inhibitors; inhibitors of Ras prenylation; dual FPT/GGPT inhibitors; sulfonamido tricycles as FPT inhibitors; farnesyl protein transferase inhibitors.

*Corresponding author.

0968-0896/98/\$19.00 © 1998 Elsevier Science Ltd. All rights reserved.
 PII: S0968-0896(98)00026-1

in these FPT inhibitors may have disadvantages in the development of such compounds as therapeutic agents. Recently, our laboratories have reported on the discovery of Sch 44342 (I) as a novel, nonpeptidic, non-thiol-containing selective FPT inhibitor.¹⁴ As part of a structure-activity study based on this lead series,¹⁵ it was of interest to determine the effect of shifting the nitrogen atom in the pendant 4-piperidine ring of I, to the adjoining position thereby rendering the molecule non-symmetrical and placing the *N*-substituents in two different spatial locations relative to the top benzocycloheptapyridine tricycle; we report here the synthesis of such geometric isomers IIa-b and IIIa-b, which contain a 3-piperidino or 3-pyrrolidino ring.¹⁶ The FPT inhibition

activities of various *N*-acyl and *N*-sulfonamido derivatives of these novel tricycles are reported.

Chemistry

The synthesis of the novel heterocycles II and III are shown in Scheme 1. Addition of the union derived from *N*-methyl-2-piperidinone or *N*-benzyl-2-pyrrolidinone to the known tricyclic ketone I (R = H or Br)^{17,18} followed by acid catalyzed dehydration of the resulting diastereoisomeric mixture of alcohols 2a-c affords the olefinic *Z*-amides 3a-c and the *E*-amides 4a-c. Dehydration of the individual diastereoisomers of 2a-c gave the same ratio of 3a-c/4a-c.^{19a}

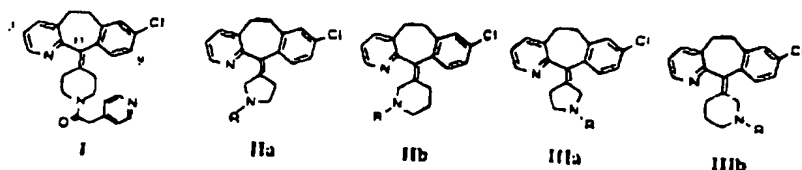
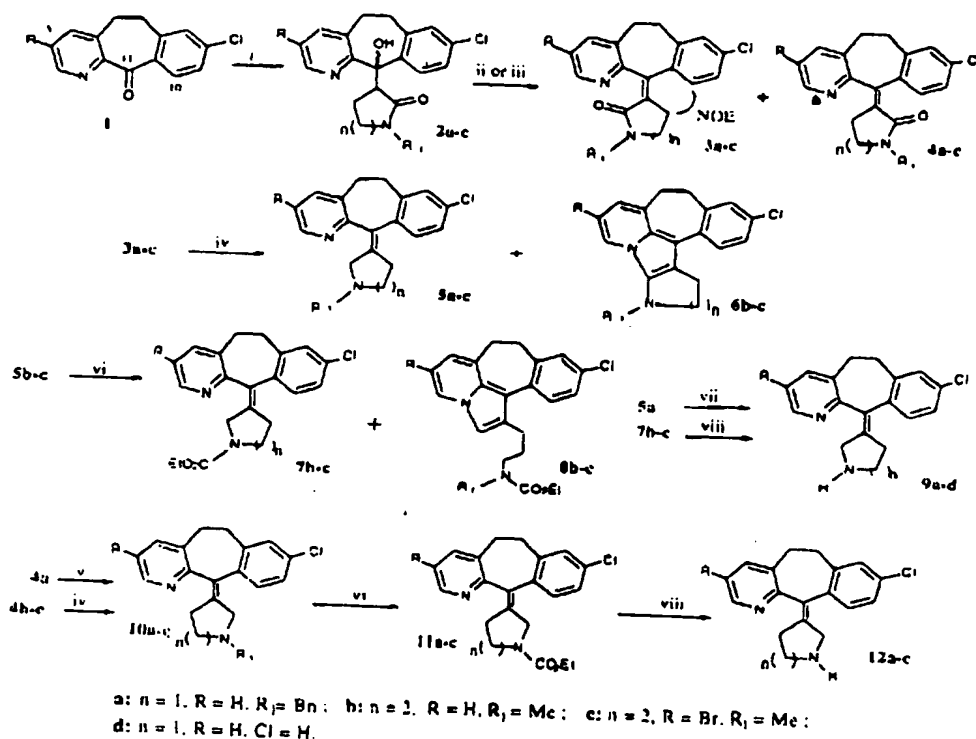


Figure 1.



Scheme 1. Reagents: (i) *N*-Methyl-2-piperidinone or *N*-benzyl-2-pyrrolidinone, LDA, THF; (ii) concd sulfuric acid; (iii) propionic acid/*p*-TsOH; (iv) LAH in THF; (v) LAH in ether; (vi) ClCO₂Et, toluene, triethylamine, 80°C; (vii) 10% Pd/C, 1,4-cyclohexadiene, acetic acid-methanol; (viii) concd HCl, 80°C.

Reduction of the lactam **3a** with LAH in THF afforded only the desired amine **5a**. LAH reduction of the lactams **3b-c** on the other hand, afforded the desired amines **5b-c** and also the novel rearrangement products **6b-c**.^{19b} LAH reduction of lactams **4b-c** in THF afforded the *E*-piperidines **10b-c**. Under these same conditions, **4a** was converted into the isomeric amines **10a** and **5a** in a 1:1 ratio; however, **10a** was formed selectively when the LAH reduction was carried out in ether.

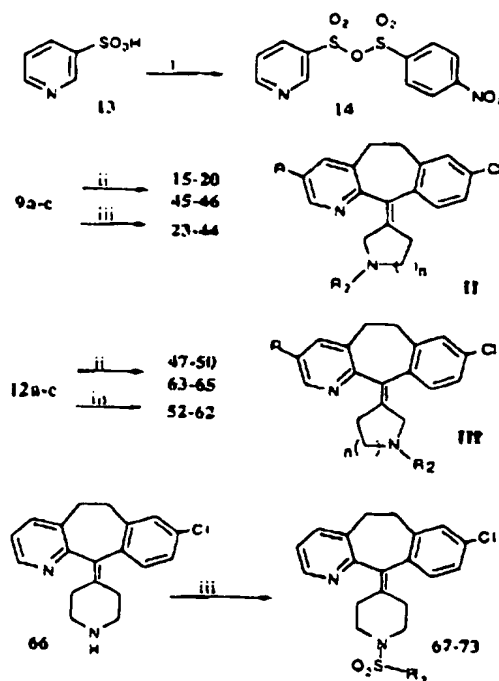
N-Dealkylation of the *E*-isomers **10a-c** with ethyl chloroformate afforded the carbamates **11a-c**, which were hydrolyzed under acidic conditions to the desired *E*-amines **12a-c**.^{19b} Under the same conditions, *N*-dealkylation of the *Z*-isomers **5b-c** afforded the expected carbamates **7b-c** and the novel indolizidine re-arrangement products **8b-c**; *N*-dealkylation of **5a** using the same reaction conditions favors exclusively the formation of the rearrangement product. The final *Z*-amines **9a-c** were obtained by acid hydrolysis of the carbamates **7b-c** and by careful hydrogenolysis of **5a**; catalytic hydrogenation of **5a** under less controlled conditions afforded **9-d**, the product of hydrogenolyses of both the *N*-benzyl and the 8-chloro groups.

The *Z*- and *E*-amines **9a-d** and **12a-c** were acylated with various carboxylic acids using standard carbodiimide reaction conditions to obtain the *N*-acyl derivatives **15-22**, and **47-50** in the piperidine series, and **45-46** and **63-65** in the pyrrolidine series. Similarly, the *N*-sulfonamido derivatives **23-40**, and **52-60** in the piperidine series and **41-44** and **61-62** in the pyrrolidine series were prepared by conventional sulfonation employing the appropriate sulfonyl chloride and Et₃N in methylene chloride.^{19c,20} Miscellaneous derivatives **21**, **22**, and **51** were obtained from the amines **9b** and **12b**. For comparison purposes, a few sulfonamides **67-73** in the lead series I were prepared from **66**.

Biology

Compounds **15-73** were tested in an FPT assay; details of this assay have been described previously.¹⁴ The assay measures the inhibition of FPT catalyzed transfer of [³H]farnesyl group from [³H]farnesyl-pyrophosphate to H-Ras-CVLS. Results of these assays are given in Tables 1-3.

Acyl derivatives of the *Z*- and *E*-isomers in both the 3-piperidino (**15-22** and **47-50**) and 3-pyrrolidino series (**45-46** and **63-65**) are generally less active as FPT inhibitors relative to acyl derivatives in the 4-piperidino series such as **1**.^{14,15} The 3-pyridylacetyl derivatives **16** and **47**, and the 4-thiopyridylacetyl derivatives **45** and **63**, are weakly active (IC₅₀ 4-7 μM). Thus far, no clear SAR is evident from the acyl derivatives.



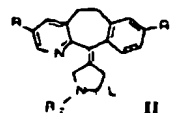
R = H, Br; for R₂ see Tables 1 and 2; for R₃ see Table 3

Scheme 2. Reagents: (i) *p*-Nitrobenzenesulfonyl chloride, pyridine, 0°C; (ii) ArCOOH, EDCI, HOBT, DMF, 0°C; (iii) Method A: ArSO₂Cl, pyridine, 0°C; Method B (Ref. 16c): **14**, pyridine, 0°C.

Sulfonamido derivatives of the *Z*- and *E*-isomers in both the 3-piperidino (**23-40** and **52-60**) and 3-pyrrolidino series (**41-44** and **61-62**) are generally more active than sulfonamido derivatives of the 4-piperidino series (compounds **67-73**) and follow an opposite SAR. For example the methyl sulfonamide of **II** (compound **23**) is inactive while the same derivative of **I** (compound **67**) is active in the FPT assay; the aromatic sulfonamides of **II** (compounds **24**, **36**, and **37**) are more active than the corresponding derivatives of **I** (compounds **68**, **72**, and **73**).

Sulfonamides **52**, **57**, **59**, **60** of the *E*-isomers are 10 times less active than the corresponding *Z*-compounds **24**, **3**, **36**, and **38**. The discussion that follows below concerns the sulfonamides of the *Z*-isomer in the 3-piperidine and 3-pyrrolidine series **II**.

The activity of the phenylsulfonamide **24** was lost by introducing *para*-substituents on the phenyl ring (e.g. **25-30**). The loss in activity is not attributable to the electronic nature of the substituent since both electron withdrawing and donating groups give rise to less

Table 1. Structure-activity of *Z*-piperidine and pyrrolidine derivatives

No.	n	R	R ₁	R ₂	Formula ^a	mp (°C) ^b	FPT Activity	
							IC ₅₀ (μM)	%Inhib. (μM) ^c
15	2	H	Cl	3-Pyridyl-CO-	C ₂₅ H ₂₂ ON ₃ Cl			> 14
16	2	H	Cl	3-Pyridyl-CH ₂ CO-	C ₂₆ H ₂₄ ON ₃ Cl		7.8	
17	2	H	Cl	4-Pyridyl-CH ₂ CO-	C ₂₆ H ₂₄ ON ₃ Cl			9 (14)
18	2	H	Cl	Phenyl-CO-	C ₂₆ H ₂₃ ON ₂ Cl	215-216		NA
19	2	H	Cl	Phenyl-CH ₂ CO-	C ₂₇ H ₂₅ ON ₂ Cl			> 14
20	2	H	Cl	Phenyl-CH ₂ CH ₂ CO-	C ₂₈ H ₂₇ ON ₂ Cl			NA
21	2	H	Cl	Phenyl-NH-CO-	C ₂₆ H ₂₄ ON ₂ Cl	184-185		10 (46)
22	2	H	Cl	Phenyl-S-CO-	C ₂₆ H ₂₃ ON ₂ ClS	187-188		6 (13)
23	2	H	Cl	CH ₃ SO ₂ -	C ₂₆ H ₂₁ O ₂ N ₂ ClS	189-190		15 (15)
24	2	H	Cl	Phenyl-SO ₂ -	C ₂₇ H ₂₃ O ₂ N ₂ ClS		0.71	
25	2	H	Cl	<i>p</i> -Acetamido-Phenyl-SO ₂ -	C ₂₇ H ₂₆ O ₃ N ₂ ClS	162-163		NA
26	2	H	Cl	<i>p</i> -Methoxy-Phenyl-SO ₂ -	C ₂₈ H ₂₅ O ₃ N ₂ ClS	160-161		33 (42)
27	2	H	Cl	<i>p</i> -Nitro-Phenyl-SO ₂ -	C ₂₇ H ₂₃ O ₄ N ₃ ClS	178-179		33 (42)
28	2	H	Cl	<i>p</i> -Fluoro-Phenyl-SO ₂ -	C ₂₇ H ₂₃ O ₂ N ₂ FS	173-174	1.34	
29	2	H	Cl	4-Methyl-Phenyl-SO ₂ -	C ₂₆ H ₂₅ O ₂ N ₂ ClS			35 (13)
30	2	H	Cl	2,4,6-Tri-Me-Phenyl-SO ₂ -	C ₂₈ H ₂₉ O ₂ N ₂ ClS	227-229		12 (12)
31	2	H	Cl	Phenyl-CH ₂ SO ₂ -	C ₂₆ H ₂₃ O ₂ N ₂ ClS	198-199		13 (13)
32	2	H	Cl	2-Thienyl-SO ₂ -	C ₂₂ H ₂₁ O ₂ N ₂ ClS ₂		0.44	
33	2	H	Cl	5-Chloro-2-Thienyl-SO ₂ -	C ₂₃ H ₂₀ O ₂ N ₂ ClS ₂	154-155	0.19	
34	2	H	Cl	5-Carboxy-2-Thienyl-SO ₂ -	C ₂₆ H ₂₁ O ₄ N ₂ ClS	228-229		47 (40)
35	2	H	Cl	5-CO ₂ CH ₃ -2-Thienyl-SO ₂ -	C ₂₅ H ₂₃ O ₄ N ₂ ClS	134-136	4.4	
36	2	H	Cl	3-Pyridyl-SO ₂ -	C ₂₄ H ₂₂ O ₂ N ₂ ClS	158-159	0.97	
37	2	Br	Cl	2-Thienyl-SO ₂ -	C ₂₃ H ₂₀ O ₂ N ₂ BrClS ₂	183-184	0.84	
38	2	Br	Cl	5-Chloro-2-Thienyl-SO ₂ -	C ₂₃ H ₁₉ O ₂ N ₂ BrCl ₂ S ₂	165-167	0.47	
39	2	Br	Cl	Phenyl-SO ₂ -	C ₂₅ H ₂₃ O ₂ N ₂ BrClS	184-185	0.58	
40	2	Br	Cl	5-Cl-1,3-diMe-4-Pyrazole-SO ₂ -	C ₂₄ H ₂₃ O ₂ N ₄ BrCl ₂ S	251-252		NA
41	1	H	Cl	Phenyl-SO ₂ -	C ₂₃ H ₂₁ O ₂ N ₂ ClS ^d		0.59	
42	1	H	H	Phenyl-SO ₂ -	C ₂₄ H ₂₂ O ₂ N ₂ S ^d		2.8	
43	1	H	Cl	2-Thienyl-SO ₂ -	C ₂₂ H ₁₉ O ₂ N ₂ ClS ^d		0.52	
44	1	H	H	2-Thienyl-SO ₂ -	C ₂₂ H ₂₀ N ₂ S ^d		3.3	
45	1	H	Cl	4-Pyridyl-S-CH ₂ -CO-	C ₂₅ H ₂₃ ON ₂ ClS ^d		4.2	
46	1	H	Cl	4-Pyridyl-CH ₂ CO-	C ₂₅ H ₂₂ ON ₂ Cl			37 (14)

^aExcept where noted, elemental analysis within 0.4% of theoretical values was obtained.

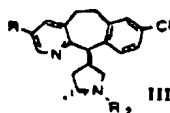
^bMelting points are uncorrected; no entries indicates that the compound is amorphous.

^cSee Refs 14 and 21 for assay details; NA indicates that no inhibition activity was observed.

^dHigh-resolution mass spectra data was obtained.

potent compounds. Heteroaromatic sulfonamides, such as the 2-thienyl analogues 32-35 and the 3-pyridyl derivative 36 are potent FPT inhibitors, with the 5-chloro-2-thienyl analogue 33 displaying an IC₅₀=0.19 μM. Incorporation of a 3-bromo substituent as in 37-39 does not have a significant effect on the FPT activity: in contrast to this, an 8-chloro substituent enhances the FPT inhibition activity sixfold as in 41, 43 versus 42, 44.

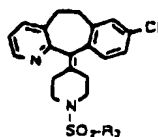
Since prenylation by GGPT is common to many cellular proteins, selectivity in FPT versus GGPT inhibition has been an important criterion for the development of an FPT inhibitor as an antitumor agent. A selected number of the above FPT inhibitors were therefore evaluated in a GGPT assay, which measures the ability of a compound to inhibit GGPT catalyzed transfer of the [³H]-geranyl-geranyl group from [³H]-geranyl-geranyl pyrophosphate to H-Ras-CVLL. A few compounds from

Table 2. Structure–activity of *E*-piperidine and pyrrolidine derivatives

No.	n	R	R ₂	Formula ^a	mp (°C) ^b	FPT Activity ^c	
						IC ₅₀ (μM)	% Inhib. (μM)
47	2	H	3-Pyridyl-CH ₂ CO-	C ₂₆ H ₂₄ ON ₃ Cl	157–158	5.1	
48	2	H	4-Pyridyl-CH ₂ CO-	C ₂₆ H ₂₄ ON ₃ Cl			42 (14)
49	2	H	3-Pyridyl-CH=CHCO-	C ₂₇ H ₂₄ ON ₃ Cl	165–166		8 (45)
50	2	H	Phenyl-CH ₂ CH ₂ CO-	C ₂₈ H ₂₇ ON ₃ Cl			27 (45)
51	2	H	<i>p</i> -NO ₂ -Phenyl-S-	C ₂₅ H ₂₂ O ₂ N ₃ ClS	173–174		12 (43)
52	2	H	Phenyl-SO ₂ -	C ₂₅ H ₂₂ O ₂ N ₃ ClS	235–236	3.3	
53	2	H	<i>p</i> -Acetamido-Phenyl-SO ₂ -	C ₂₇ H ₂₆ O ₃ N ₃ ClS	147–149	33.5	
54	2	H	<i>p</i> -Methoxy-Phenyl-SO ₂ -	C ₂₆ H ₂₅ O ₃ N ₃ ClS	168–169		32 (42)
55	2	H	<i>p</i> -Nitro-Phenyl-SO ₂ -	C ₂₅ H ₂₂ O ₄ N ₃ ClS	232–233		29 (40)
56	2	H	<i>p</i> -Fluoro-Phenyl-SO ₂ -	C ₂₅ H ₂₂ O ₂ N ₃ ClFS	154–155		45 (43)
57	2	H	2-Thienyl-SO ₂ -	C ₂₃ H ₂₁ O ₂ N ₃ ClS	254–255	4.8	
58	2	H	5-PhCONHCH ₂ -2-Thienyl-SO ₂ -	C ₃₁ H ₂₉ O ₃ N ₃ ClS ₂			17 (34)
59	2	H	3-Pyridyl-SO ₂ -	C ₂₄ H ₂₂ O ₂ N ₃ ClS	214–215	8.8	
60	2	Br	5-Chloro-2-Thienyl-SO ₂ -	C ₂₃ H ₁₉ O ₂ N ₃ BrCl ₂ S ₂	171–172	8.0	
61	1	H	Phenyl-SO ₂ -	C ₂₆ H ₂₁ N ₃ O ₂ ClS ^d	181 (dec)	4.0	
62	1	H	2-Thienyl-SO ₂ -	C ₂₂ H ₁₉ N ₃ O ₂ ClS ^d	173 (dec)	5.1	
63	1	H	4-Pyridyl-S-CH ₂ -CO-	C ₂₅ H ₂₂ N ₃ OCIS ^d		6.9	
64	1	H	4-Pyridyl-CH ₂ CO-	C ₂₅ H ₂₂ N ₃ OCI ^d			11 (14)
65	1	H	2-Furanyl-CO-	C ₂₅ H ₁₉ N ₃ O ₂ Cl ^d	190–192		33 (50)

^{a–c}Refer to footnotes under Table 1.

Table 3. Structure–activity of piperidino sulfonamides



No.	R ₂	Formula ^a	mp (°C) ^b	FTP Activity ^c	
				IC ₅₀ (μM)	% Inhib. (μM)
67	CH ₃ -			1.9 ^d	
68	Phenyl-	C ₂₅ H ₂₃ O ₂ N ₃ ClS	174–175		NA
69	<i>p</i> -CH ₃ -Phenyl-	C ₂₆ H ₂₅ O ₂ N ₃ ClS			NA
70	<i>p</i> -AcNH-Phenyl-	C ₂₇ H ₂₆ O ₂ N ₃ ClS	157–158		NA
71	<i>p</i> -NO ₂ -Phenyl-	C ₂₅ H ₂₂ O ₄ N ₃ ClS	230–231		> 12 ^d
72	2-Thienyl-			13 ^d	
73	3-Pyridyl-	C ₂₄ H ₂₂ O ₂ N ₃ ClS	103–105	6.6	

^{a–c}Refer to footnotes under Table 1.^dData from Ref. 15c.

this group were also evaluated in a COS assay which measures transient expression and processing (farnesylation) of H-Ras-CVLS in COS monkey kidney cells. Details of these assays have been reported previously.¹⁴

and the results are shown in Table 4. The data in Table 4 indicate that none of the compounds tested shows high selectivity for FPT versus GGPT inhibition; the GGPT inhibitory concentration for these compounds is

Table 4. Prenylation selectivity

No.	FPT ^a		GGPT		COS ^a
	IC ₅₀ (μ M)	% Inhib. (μ M)	IC ₅₀ (μ M)	% Inhib. (μ M)	
21		10 (46)	0.8		
24	0.71		2.6		2.5
25		1 (39)	2.6		
28	1.34		4.9		
32	0.44		4.4		
33	0.19			68 (4)	> 5
37	0.84			18 (37)	
39	0.58			29 (38)	
41	0.59		7.1		> 5
42	2.8			47 (50)	
43	0.52			56 (4.5)	
44	3.3			39 (49)	
16	7.8			17 (12)	

^aRefer to footnotes under Table 1.

only 4–100 times less than their FPT IC₅₀. A 3-bromo substituent decreases the GGPT inhibitory activity thereby increasing the FPT/GGPT selectivity as in 37, 39 versus 32, 24. The prenylation inhibition selectivity can be offset to favor GGPT inhibition by changing the nitrogen substituent as in the acyl derivative 21 and the sulfonamide analogue 25, which are selective GGPT inhibitors. Of the three compounds tested in the COS assay, 24 has a reasonable ratio for cell-based/in vitro enzyme FPT inhibitory activity.

Conclusions

Several conclusions are evident from the above study. Foremost, it demonstrates that the spatial location of the *N*-acyl group in the lead compound I is critical for binding of the compound to FPT; alteration in the location of this *N*-acyl functionality as in *N*-acyl derivatives of II and III leads to a marked loss in FPT inhibition activity. The *N*-sulfonamido derivatives of the *Z*-isomer II, on the other hand, are potent FPT inhibitors relative to the corresponding sulfonamido derivatives of *E*-isomer III and the lead tricycle I. These *N*-sulfonamido compounds of type II do not follow the SAR of the corresponding derivatives of the lead tricycle I. More detailed studies of the FPT active *N*-sulfonamido analogues showed that the compounds are also inhibitors of GGPT; the degree of this dual inhibition ranges from 4- to 100-fold in favor of FPT inhibition; a 3-bromo substituent increases the FPT/GGPT selectivity. These findings suggest that the binding mode of II to the FPT protein is different from that of I, and this change in the spatial location of the *N*-functionality

leads to nonselective binding resulting in dual FPT/GGPT inhibitors.

Selective inhibition of farnesylation of Ras by FPT has been an important criterion for the development of antitumor agents to control tumorigenic cell proliferation in tumors containing activated Ras.^{7,8} However, it has been recently reported that *N*-Ras, K-Ras4B and K-Ras4A are *in vitro* substrates for both FPT and GGPT;^{9,10} a more recent report demonstrated that in the presence of the potent FPT inhibitor 3-bromo-I, Ras proteins in the human colon carcinoma cell line DLD-1 are alternatively prenylated by GGPT.¹¹ In light of these reports on the alternative prenylation of *N*- and K-Ras, dual FPT/GGPT inhibitors may be required to block Ras prenylation and to control cell proliferation in tumors containing activated Ras. In summary, the present *N*-sulfonamido series II is a novel lead of non-sulfhydryl, nonpeptidic compounds that are dual FPT/GGPT inhibitors; further chemical modifications of the series are needed to attain potency and the proper balance of FPT/GGPT inhibition. The SAR developed from this study is being used to design improved FPT inhibitors of the lead compound I.

Experimental

Reactions were performed under conventional techniques: employing oven dried glassware, nitrogen atmosphere, and commercial or freshly dried/distilled solvents. Extracts of crude reaction products were dried over anhydrous magnesium sulfate (MgSO₄) or sodium sulfate (Na₂SO₄), evaporated under reduced pressure and purified by flash chromatography using Select Scientific 32-63 mesh silica gel. Melting points are uncorrected. ¹H NMR spectra were determined on a Varian VXR 200 or Gemini 300 MHz spectrometer using CDCl₃, CD₃OD, or DMSO-*d*₆ solutions and TMS as internal standard. ¹³C NMR spectra were obtained at 75 MHz with the chemical shifts reported in ppm relative to the central line of CDCl₃ (77.00 ppm). Mass spectra were determined either on Extrel 401, Jeol or VG Zab-SE mass spectrometer. Unless otherwise noted elemental analyses were within 0.4% of theoretical value.

3-Bromo-8-chloro-6,11-dihydro-11-hydroxy-11-(1-methyl-2-oxo-piperidin-3-yl)-5*H*-benzo[5,6(cyclohepta)[1,2-*b*]pyridine (2c). *n*-Butyllithium (2.5 M in hexanes, 18 mL, 45.0 mmol) was added dropwise to a solution of diisopropylamine (7.0 mL, 49.4 mmol) in THF (100 mL) at -78 °C, stirred for 30 min and *N*-methyl-2-piperidone (7.0 mL, 64 mmol) was added dropwise. The resultant solution was stirred for 30 min and then allowed to warm to -5 °C over a 60 min period. The reaction mixture was

cooled to -78°C and a solution of 3-bromo-8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-one (1, $\text{R} = \text{Br}$)¹⁸ (12 g, 37.2 mmol) in THF (200 mL) was added dropwise. The mixture was stirred at -78°C for 1 h, then warmed to -10°C over a 1 h period. Water (25 mL) was added, the mixture concentrated to ca. 100 mL, then extracted with methylene chloride (500 mL). The product crystallized on addition of acetone:ether (50 mL, 1:1). The solid was filtered, washed with ether (10 mL) and dried yielding 11.89 g of **2c**. The mother liquor was concentrated and upon chromatography using ethyl acetate:hexanes (1:3) yielded an additional 1.0 g of **2c** (79.56% total yield, mixture of diastereoisomers): MS(Cl) m/z 435 (MH^+); Anal. ($\text{C}_{19}\text{H}_{18}\text{BrClN}_2\text{O}_2$) C, H, N.

8-Chloro-6,11-dihydro-11-hydroxy-11-(1-methyl-2-oxo-piperidin-3-yl)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (2b). Reaction of *N*-methyl-2-piperidone with 8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-one (1, $\text{R} = \text{H}$)¹⁷ using the procedure for **2c** afforded **2b** (76% yield, 10:1 mixture of diastereoisomers). The diastereoisomers were isolated by chromatography. Diastereomer A (minor product), higher R_f on TLC (40% EtOAc:Hexanes): mp $164\text{--}166^{\circ}\text{C}$; ^1H NMR (300 MHz, CDCl_3) δ 8.30 (d, 1H), 7.95 (d, 1H), 7.47 (d, 1H), 7.35 (s, 1H), 7.16 (m, 2H), 7.01 (s, 1H), 3.75 (m, 2H), 3.40 (m, 2H), 3.15 (m, 5H), 2.91 (s, 3H), 1.85 (m, 1H), 1.30 (m, 1H); MS(Cl), m/z 357 (MH^+). Anal. ($\text{C}_{20}\text{H}_{21}\text{ClN}_2\text{O}_2$) C, H, N. Diastereomer B (major product) Lower R_f on TLC: mp $164\text{--}165^{\circ}\text{C}$; ^1H NMR (300 MHz, CDCl_3) δ 8.30 (d, 1H), 7.95 (d, 1H), 7.67 (s, 1H), 7.42 (d, 1H), 7.15 (m, 2H), 7.08 (s, 1H), 3.60–3.80 (m, 2H), 3.45 (m, 2H), 3.15 (m, 1H), 3.05 (m, 2H), 2.86 (s, 3H), 1.90 (m, 2H), 1.60 (m, 1H), 1.50 (m, 1H); MS(Cl) m/z 357 (MH^+); Anal. ($\text{C}_{20}\text{H}_{21}\text{ClN}_2\text{O}_2$) C, H, N.

8-Chloro-6,11-dihydro-11-hydroxy-11-(1-benzyl-2-oxo-pyrrolidin-3-yl)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (2a). Reaction of *N*-methyl-2-pyrrolidinone with 8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-one (1, $\text{R} = \text{H}$)¹⁷ using the procedure for **2c** afforded **2a**. The less polar diastereoisomer A was insoluble in warm EtOAc and was isolated as a white crystalline solid (42%): mp $164\text{--}166^{\circ}\text{C}$; ^1H NMR (300 MHz, CDCl_3) δ 8.4 (d, 1H, $J = 4.8$ Hz), 8.1 (d, 1H, $J = 8.6$ Hz), 7.6 (d, 1H, $J = 6.7$ Hz), 7.19–7.45 (m, 9H), 4.5 (apparent q, 2H, $J = 14.7$ Hz), 3.75–3.90 (m, 2H), 3.5–3.6 (m, 1H), 3.35–3.45 (m, 1H), 3.1–3.2 (m, 3H), 1.7–1.9 (m, 2H). ^{13}C NMR (75 MHz, CDCl_3) δ 172.83, 157.96, 144.33, 141.02, 140.03, 137.21, 136.95, 133.13, 132.13, 130.25, 129.78, 128.76, 128.38, 127.53, 126.22, 123.76, 49.79, 46.89, 45.17, 32.56, 31.31, 20.70. MS (Cl) m/z 385 (MH^+); Anal. ($\text{C}_{23}\text{H}_{23}\text{N}_2\text{O}_2\text{Cl}$) C, H, N. The more polar diastereoisomer B was isolated by chromatography from the EtOAc soluble fraction (solvent: 2–5%

THF/ CH_2Cl_2) as an amorphous solid (45%): ^1H NMR (300 MHz, CDCl_3) δ 8.5 (d, 1H, $J = 4.2$ Hz), 8.1 (d, $J = 8.5$ Hz), 7.8 (s, 1H), 7.6 (d, $J = 7.8$ Hz), 7.2–7.5 (m, 8H), 4.5 (apparent q, 2H, $J = 14.7$ Hz), 3.9–4.0 (m, 1H), 3.6–3.9 (m, 2H), 3.4–3.5 (m, 1H), 3.1–3.3 (m, 3H), 2.15–2.30 (m, 1H), 1.8–1.95 (m, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 172.95, 157.51, 144.00, 143.95, 141.76, 139.61, 137.67, 136.83, 133.31, 132.29, 130.72, 128.82, 128.78, 128.37, 127.59, 126.50, 123.52, 50.05, 46.91, 45.48, 32.31, 31.33, 21.02. MS (Cl) m/z 385 (MH^+); Anal. ($\text{C}_{23}\text{H}_{23}\text{N}_2\text{O}_2\text{Cl}$) C, H, N.

3-(3-Bromo-8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-methyl-2-piperidinone (3c and 4c). A solution of **2c** (11.4 g, 26.1 mmol) in concentrated sulfuric acid (100 mL) was stirred at 80°C for 4 h, then cooled to 20°C . The reaction mixture was poured into ice (300 g) and basified with 50% NaOH. The precipitated solid was filtered, washed with water (200 mL), dried and chromatographed eluting with ethyl acetate:methanol, 98:2 to yield the *Z*-isomer (**3c**) as a white solid (4.48 g, 41%): ^1H NMR δ 8.38 (s, 1H), 7.58 (s, 1H), 7.17 (s, 3H), 3.3–3.6 (m, 4H), 2.92 (s, 3H), 2.7–2.9 (m, 3H), 2.30–2.45 (m, 1H), 1.95–2.15 (m, 2H); MS(Cl) m/z 417 (MH^+); Anal. ($\text{C}_{20}\text{H}_{18}\text{BrClN}_2\text{O}$) C, H, N. The *E*-isomer (**4c**) was eluted as a white solid (4.68 g, 43%): ^1H NMR (300 MHz, CDCl_3) δ 8.46 (s, 1H), 7.61 (s, 1H), 7.14 (s, 1H), 7.10 (s, 2H), 3.25–3.60 (m, 4H), 2.94 (s, 3H), 2.70–2.90 (m, 3H), 1.80–2.20 (m, 3H); MS(Cl) m/z 417 (MH^+); Anal. ($\text{C}_{20}\text{H}_{18}\text{BrClN}_2\text{O}$) C, H, N.

Dehydration of **2b** and **2a** by the above procedure followed by chromatography afforded the following compounds **3b**, **4b** and **3a**, **4a**

(Z)-3-(8-Chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-methyl-2-piperidinone (3b). White solid (40%): mp $179\text{--}181^{\circ}\text{C}$; ^1H NMR (300 MHz, CDCl_3) δ 8.35 (d, 1H), 7.55 (d, 1H), δ 8.35 (d, 1H), 7.55 (d, 1H), 7.2 (m, 2H), 7.0–7.1 (m, 2H), 3.3–3.6 (m, 4H), 2.92 (s, 3H), 2.7–2.9 (m, 3H), 2.0–2.2 (m, 2H), 1.90 (m, 1H); MS(Cl) m/z 339 (MH^+).

(E)-3-(8-Chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-methyl-2-piperidinone (4b). White solid (40%): mp 133°C ; ^1H NMR (300 MHz, CDCl_3) δ 8.40 (d, 1H), 7.44 (d, 1H), 7.18 (d, 1H), 7.0–7.15 (m, 3H), 3.3–3.6 (m, 4H), 2.92 (s, 3H), 2.7–2.9 (m, 3H), 2.0–2.2 (m, 2H), 1.90 (m, 1H); MS(Cl) m/z 339 (MH^+).

(Z)-3-(8-Chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-benzyl-2-pyrrolidinone (3a). (83% for **3a/4a** combined): mp $178\text{--}180^{\circ}\text{C}$; ^1H NMR (300 MHz, CDCl_3) δ 8.5 (d, 1H, $J = 5.1$ Hz), 7.2–7.6 (m, 10H), 4.63 (AB quartet, 2H, $J = 14.4$ Hz), 3.25–3.60 (m,

5H), 2.85–3.10 (m, 2H), 2.45–2.60 (m, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 166.81, 156.22, 146.55, 143.01, 138.21, 138.14, 136.27, 138.83, 133.48, 133.22, 131.46, 131.42, 128.52, 128.17, 128.09, 127.45, 125.32, 122.77, 46.95, 42.96, 31.42, 31.39, 24.60; MS(Cl), m/z 401 (MH^+); Anal. ($\text{C}_{25}\text{H}_{23}\text{N}_2\text{OCl}$), C, H, N.

(*E*)-3-(8-Chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-benzyl-2-pyrrolidinone (4a). Mp 90–100°C; ^1H NMR (300 MHz, CDCl_3) δ 8.5 (d, 1H, $J = 5.1$ Hz), 7.6 (d, 1H, $J = 7.2$ Hz), 7.2–7.5 (m, 9H), 4.5 (AB quartet, 2H, $J = 14.7$ Hz), 3.25–3.58 (m, 4H), 3.1–3.21 (m, 1H), 2.85–3.10 (m, 2H), 2.59–2.65 (m, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 166.49, 157.02, 146.81, 143.72, 139.22, 136.77, 136.52, 136.45, 133.83, 132.23, 131.52, 130.27, 129.06, 128.84, 128.66, 127.78, 126.52, 123.16, 47.37, 43.33, 32.32, 30.78, 24.62; MS(Cl), m/z 401 (MH^+); Anal. ($\text{C}_{25}\text{H}_{23}\text{N}_2\text{OCl}$), C, H, N.

(*Z*)-3-Bromo-8-chloro-6,11-dihydro-11-(1-methyl-3-piperidinylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (5c) and 7-bromo-12-chloro-1,2,3,4,9,10-hexahydro-4-methyl-benzo[4,5]cyclohepta[1,2,3-*h*]pyrido[3,2-*b*]indolizine (6c). LAH (110 mg, 2.78 mmol) was added to 3c (1.0 g, 2.39 mmol) in THF (10 mL) at -5°C and the resultant solution was stirred at this temperature for 2 h. The reaction was quenched by addition of ethyl acetate (2 mL) followed by a solution of 10% potassium sodium tartrate tetrahydrate (20 mL) and 10% sodium hydroxide (5 mL). The mixture was extracted with methylene chloride (150 mL) and chromatographed on silica gel eluting with hexanes:ethylacetate 5:1 yielding the title compound (6c) as a solid, which was recrystallized from methanol:ether as yellow needles (240 mg, 25%); mp 155–156°C; ^1H NMR (300 MHz, CDCl_3) δ 7.83 (s, 1H), 7.55 (d, 1H), 7.30 (s, 1H), 7.25 (d, 1H), 6.58 (s, 1H), 3.20–3.40 (m, 4H), 2.70–2.90 (m, 4H), 2.67 (s, 3H), 1.80–1.95 (m, 2H); MS(Cl) m/z 402 (MH^+); Anal. ($\text{C}_{20}\text{H}_{18}\text{BrClN}_2$) C, H, N. The title product (5c) was eluted with ethyl acetate:methanol (97:3) containing 1% NH_4OH , yielding the product as a tan solid (480 mg, 50%); mp 160–161°C; ^1H NMR (300 MHz, CDCl_3) δ 8.45 (s, 1H), 7.56 (s, 1H), 7.10–7.17 (m, 3H), 3.35–3.50 (m, 3H), 2.60–2.95 (m, 2H), 2.78 (s, 3H), 2.0–2.3 (m, 5H), 1.75 (m, 2H); MS(Cl) m/z 403 (MH^+) Anal. ($\text{C}_{20}\text{H}_{20}\text{BrClN}_2$) C, H, N.

LAH reduction of 3a and 3b by the above procedure afforded 5a, 5b, and 6b.

(*Z*)-8-Chloro-6,11-dihydro-11-(1-methyl-3-piperidinylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (5b). White solid (50%); ^1H NMR (300 MHz, CDCl_3) δ 8.39 (d, 1H), 7.40 (d, 1H), 7.0–7.2 (m, 4H), 3.50 (m, 3H), 2.79 (s, 3H), 2.7–2.9 (m, 3H), 2.42 (m, 1H), 2.21 (m, 4H), 1.6–1.8 (m, 2H); MS(Cl) m/z 325 (MH^+).

12-Chloro-1,2,3,4,9,10-hexahydro-4-methyl-benzo[4,5]cyclohepta[1,2,3-*h*]pyrido[3,2-*b*]indolizine (6b). Yellow crystals (25%); mp 170–172°C; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 7.70 (d, 1H), 7.49 (d, 1H), 7.26 (s, 1H), 7.23 (d, 1H), 6.51 (m, 1H), 6.46 (m, 1H), 3.17 (m, 4H), 2.70 (m, 4H), 2.66 (s, 3H), 1.80–1.95 (m, 2H); MS(Cl) m/z 322 (MH^+); X-ray; HRMS calcd (MH^+) for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{Cl}$ 322.1237, measured 322.1233.

(*Z*)-8-Chloro-6,11-dihydro-11-(1-benzyl-3-pyrrolidinene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (5a). (54%) ^1H NMR (300 MHz, CDCl_3) δ 8.4 (d, 1H, $J = \sim 5$ Hz), 7.0–7.4 (m, 10H), 3.55–3.75 (m, 3H), 3.18–3.42 (m, 3H), 2.68–2.94 (m, 4H), 2.5–2.58 (m, 1H), 2.2–2.3 (m, 1H). ^{13}C (75 MHz, CDCl_3) δ 156.52, 146.68, 144.34, 140.58, 139.22, 139.11, 138.11, 132.99, 132.91, 131.63, 130.48, 129.04, 128.46, 127.14, 126.55, 122.20, 60.99, 59.39, 53.88, 32.53, 31.68, 31.54. MS(Cl) m/z 386 (MH^+). HRMS calcd. for $\text{C}_{25}\text{H}_{24}\text{N}_2\text{Cl}$: 387.1628; F und, 387.1609. Anal. ($\text{C}_{25}\text{H}_{23}\text{N}_2\text{Cl} \times 0.25 \text{ mol H}_2\text{O}$) C, H, N.

(*Z*)-Ethyl-3-(3-bromo-8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-piperidinecarboxylate (7c) and ethyl-[3-(5-bromo-10-chloro-7,8-dihydro-benzo[4,5]cyclohepta[1,2,3-*h*]indolizin-1-yl)propyl]-methylcarbamate (8c). Ethylchloroformate (1.0 mL, 10.4 mmol) and triethylamine (1.0 mL, 13.6 mmol) were added to a solution of 5c in toluene (20 mL) at 0°C , then stirred at 70°C for 3 h. The solvent was evaporated under reduced pressure, and the residual oil extracted with CH_2Cl_2 (50 mL), washed with H_2O (20 mL) and chromatographed on silica gel. Elution with hexanes:ethylacetate (5:1) yielded an oil which crystallized on standing from ether to afford 8c as yellow crystals (600 mg, 46.1%); mp 112–114°C; ^1H NMR (300 MHz, CDCl_3) δ 7.86 (s, 1H), 7.43 (d, 1H), 7.15–7.25 (m, 3H), 6.53 (s, 1H), 4.12 (q, 2H), 3.32 (m, 2H), 2.90 (m, 6H), 2.85 s, 3H), 1.80–2.0 (m, 2H), 1.24 (t, 3H); MS(Cl) m/z 475 (MH^+); Anal. ($\text{C}_{23}\text{H}_{24}\text{BrClN}_2\text{O}_2$) C, H, N. The second title compound 7c eluted from the column yielding a solid, which crystallized from ether:methylene chloride as white crystals (510 mg, 40.8%); mp 182–183°C; ^1H NMR (300 MHz, CDCl_3) δ 8.47 (s, 1H), 7.62 (s, 1H), 7.11–7.17 (m, 3H), 4.55 (d, 1H), 4.02 (q, 2H), 4.0 (m, 1H), 3.75 (m, 1H), 3.3 (m, 2H), 3.1 (m, 1H), 2.82 (m, 2H), 2.55 (m, 1H), 2.32 (m, 1H), 1.75 (t, 3H), 1.0 (m, 2H); MS(Cl) m/z 461 (MH^+); Anal. ($\text{C}_{22}\text{H}_{22}\text{BrClN}_2\text{O}_2$) C, H, N. Ethylchloroformate dealkylation of 5b using the above procedure afforded 7b and 8b.

(*Z*)-Ethyl-3-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-piperidinecarboxylate (7b). White solid (45%); ^1H NMR (300 MHz, CDCl_3) δ 8.45 (d, 1H), 7.43 (d, 1H), 7.13 (m, 4H), 4.55 (d, 1H), 4.02 (q, 2H), 4.0 (m, 1H), 3.75 (m, 1H), 3.30 (m, 2H), 3.1

(m, 1H), 2.82 (m, 2H), 2.55 (m, 1H), 2.32 (m, 1H), 1.75 (t, 3H), 1.0 (m, 2H); MS(Cl) m/z 383 (MH⁺).

Ethyl-[3-(10-chloro-7,8-dihydro-benzo[4,5]cyclohepta[1,2,3-*h*]indolizin-1-yl) propyl]methylcarbamate (8b). White solid (44%); ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.08 (d, 1H), 7.57 (s, 1H), 7.50 (d, 1H), 7.29 (d, 1H), 7.25 (d, 1H), 6.48 (m, 2H), 4.0 (q, 2H), 3.32 (m, 2H), 2.90 (m, 6H), 2.79 (s, 3H), 1.85 (m, 2H), 1.15 (t, 3H); MS(Cl) m/z 397 (MH⁺). HRMS calcd (MH⁺) for C₂₃H₂₆N₂O₂Cl 397.1683, measured 397.1681.

(Z)-3-Bromo-8-chloro-6,11-dihydro-11-(3-piperidinylidene)-5H-benzo[5,6]cyclohepta[1,2-*b*]pyridine (9c). A solution of 7c (400 mg, 0.866 mmol) in conc HCl (5 mL) was stirred at 100 °C overnight, then cooled to 0 °C, poured into ice (10 g) and basified with 30% NaOH. The mixture was extracted with CH₂Cl₂ (100 mL), and the organic layer was dried, filtered, and evaporated yielding 9c as a white foam (320 mg, 94.8%); ¹H NMR (300 MHz, CDCl₃) δ 8.37 (s, 1H), 7.40 (d, 1H), 7.14–7.34 (m, 3H), 3.46 (m, 4H), 2.86 (m, 4H), 2.38 (m, 2H), 1.75 (m, 1H), 1.62 (m, 1H); MS(Cl) m/z 389 (MH⁺); Anal. (C₁₉H₁₈BrClN₂) C, H, N.

Hydrolysis of 7b by this procedure afforded 9b.

(Z)-8-Chloro-6,11-dihydro-11-(3-piperidinylidene)-5H-benzo[5,6]cyclohepta[1,2-*b*]pyridine (9b). White solid (90%); mp 170–171 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.38 (d, 1H), 7.41 (d, 1H), 7.05–7.30 (m, 4H), 3.45 (m, 4H), 2.88 (m, 4H), 2.40 (m, 2H), 1.75 (m, 1H), 1.62 (m, 1H); MS (Cl) m/z 311 (MH⁺); Anal. (C₁₉H₁₆ClN₂) C, H, N.

(Z)-8-Chloro-6,11-dihydro-11-(3-pyrrolylidene)-5H-benzo[5,6]cyclohepta[1,2-*b*]pyridine (9a). To a two-necked flask equipped with a reflux condenser and a three-way valve (allowing for evacuation under vacuum and purging with nitrogen) was added 5a (1.29 mmol, 500 mg), MeOH (20 mL), acetic acid (5 mL), cyclohexadiene (5 mL), and 10% Pd/C (210 mg). After three cycles of evacuation-nitrogen purging was performed, an empty balloon was placed on top of the condenser so as to expand as hydrogen was evolved. The mixture was heated carefully to 70 °C at which time hydrogen evolution began. If starting material was still present by TLC after 1 h, a full hydrogen balloon was placed over the reaction mixture. The reduction was continued at ~40 °C for an additional 1 h (or until complete by TLC). The contents were then filtered through celite, and the effluent was concentrated under reduced pressure. Toluene was added and the material was evaporated once again to remove the HOAc. Chromatography on SiO₂ using (5% MeOH:CH₂Cl₂ increasing gradually to 10% MeOH:CH₂Cl₂:1% NH₄OH) gave 9a (221 mg, 58%) as a tan

solid; ¹H NMR (300 MHz, CDCl₃) δ 8.3 (d, 1H, *J* = 4.7 Hz), 7.3 (d, 1H, *J* = 6.7 Hz), 7.2 (d, 1H, *J* = 7.8 Hz), 7.10–7.19 (m, 2H), 7.06 (d, 1H, *J* = 4.8 Hz), 7.03 (d, 1H, *J* = 7.8 Hz), 4.09 (d, 1H, *J* = 16.4 Hz), 3.2–3.4 (m, 3H, containing a d, *J* = 16.2 Hz), 3.12–3.18 (m, 1H), 2.6–2.9 (m, 5H), 2.12–2.22 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 154.68, 146.49, 139.56, 138.93, 138.75, 137.17, 135.51, 134.01, 128.71, 128.42, 126.74, 126.55, 122.74, 48.68, 44.80, 32.95, 31.64, 30.09; MS(Cl) 296 (MH⁺); Anal. (C₁₈H₁₄NCl × 0.25 mol H₂O) C, H, N.

(Z)-6,11-Dihydro-11-(3-pyrrolylidene)-5H-benzo[5,6]cyclohepta[1,2-*b*]pyridine (9d). Compound 5a (2.3 g, 5.95 mmol) was dissolved in a solution of MeOH (70 mL) and acetic acid (8 mL) along with Pd(OH)₂ catalyst (800 mg). The mixture was pressurized to 35 psi with hydrogen gas, and shaken for 3 h. The catalyst was removed by filtration through celite, and the effluent was concentrated under reduced pressure and chromatographed on silica gel eluting with 5% MeOH:CH₂Cl₂ increasing gradually to 10% MeOH:CH₂Cl₂:1% NH₄OH, which afforded 1.49 g (84%) of material as a light tan solid. ¹H NMR (CDCl₃) δ 8.35 (bs, 1H), 7.0–7.4 (m, 6H), 4.5 (d, 1H, *J* = 16.3 Hz), 3.7 (d, 1H, *J* = 16.4 Hz), 3.2–3.5 (m, 4H), 2.7–3.0 (m, 3H), 2.4–2.50 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 155.48, 146.45, 139.95, 138.79, 138.63, 138.49, 135.59, 133.82, 128.82, 128.47, 128.10, 126.46, 122.54, 49.58, 45.62, 32.80, 31.72, 31.18; MS(Cl) m/z 263 (MH⁺).

(E)-3-Bromo-8-chloro-6,11-dihydro-11-(1-methyl-3-piperidinylidene)-5H-benzo[5,6]cyclohepta[1,2-*b*]pyridine (10c). LAH (470 mg, 11.9 mmol) was added to a solution of 4c (3.4 g, 8.15 mmol) in THF (40 mL, anhydrous) at 0 °C. The solution was stirred at 0 °C for 5 h, then water (5 mL), 10% potassium sodium tartrate tetrahydrate (20 mL), 10% sodium hydroxide (5 mL), and CH₂Cl₂ (150 mL) were added sequentially. The crude product obtained from the organic layer was chromatographed on silica gel eluting with EtOAc:MeOH (98:2) yielding the product as a white solid (1.3 g, 40%); mp 140–141 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.45 (s, 1H), 7.62 (s, 1H), 7.16 (s, 1H), 7.14 (d, 1H), 7.05 (d, 1H), 3.50 (m, 3H), 3.0 (m, 1H), 2.75–2.80 (m, 3H), 2.26 (m, 2H), 2.23 (s, 3H, NCH₃), 2.20 (m, 1H), 1.75 (m, 2H); MS(Cl) m/z 403 (MH⁺); Anal. (C₂₀H₂₀BrClN₂) C, H, N.

LAH reduction of 4b by the above procedure afforded 10b.

(E)-8-Chloro-6,11-dihydro-11-(1-methyl-3-piperidinylidene)-5H-benzo[5,6]cyclohepta[1,2-*b*]pyridine (10b). White solid (45%); mp 125–126 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.38 (d, 1H), 7.45 (d, 1H), 7.13 (s, 1H), 7.06–7.12 (d, 1H), 7.06 (d, 1H), 3.50 (m, 3H), 3.0 (m, 1H), 2.78–2.80 (m, 3H), 2.25 (m, 2H), 2.23 (s, 3H).

NCH₃), 2.20 (m, 1H), 1.75 (m, 2H); MS(Cl), *m/z* 325 (MH⁺); Anal. (C₂₀H₂₁N₃Cl) C, H, N.

(*E*)-8-Chloro-6,11-dihydro-11-(1-benzyl-3-pyrrolylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (10a). To a two-necked flask containing LAH (27.7 mmol, 1.04 g) was added Et₂O (75 mL) under a N₂ atmosphere. The solution was cooled to 0°C, and a THF solution of 4a (5.49 mmol, 2.20 g) was added via syringe. After the addition was complete a heterogeneous brick red solution resulted. TLC analysis after 2 h indicated all the starting material had been consumed, with no isomerization taking place. The reaction mixture was quenched with EtOAc and MeOH, followed by the addition of 1% NaOH. The aqueous portion was extracted 4 × 75 mL with EtOAc then with EtOAc:THF (4:1), and the combined organics were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure to give a reddish foam. Chromatography on SiO₂ using (15% acetone:EtOAc increasing gradually to 5% MeOH:EtOAc) gave 10a (1.08 g, 51%) as a tan solid: ¹H NMR (300 MHz, CDCl₃) δ 8.4 (d, 1H, *J* = 5 Hz), 7.0–7.4 (m, 10H), 3.5–3.7 (m, 3H), 3.20–3.42 (m, 3H), 2.70–2.92 (m, 4H), 2.48–2.58 (m, 1H), 2.18–2.28 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 156.21, 146.37, 146.15, 144.01, 140.25, 138.89, 138.78, 137.79, 132.68, 132.58, 131.31, 130.14, 128.72, 128.12, 126.81, 126.21, 121.81, 60.67, 59.06, 53.55, 32.21, 31.36, 31.18; MS (Cl) *m/z* 387 (MH⁺); Anal. (C₂₅H₂₃N₃Cl) (0.25 mol H₂O) C, H, N.

(*E*)-Ethyl-3-(3-bromo-8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-piperidinecarboxylate (11c). Ethylchloroformate (0.5 mL, 5.2 mmol) and triethylamine (1.0 mL, 13.6 mmol) were added to a solution of 10c in toluene (15 mL) at 0°C then stirred at 70°C for 3 h. The solvent was evaporated under reduced pressure, and the residual oil extracted with CH₂Cl₂ (50 mL) and washed with H₂O (20 mL). The crude product isolated from the organic extract was chromatographed on silica gel eluting with hexanes:ethylacetate, then crystallized from ether as white crystals (230 mg, 51%); mp 186–187°C; ¹H NMR (300 MHz, CDCl₃) δ 8.46 (s, 1H), 7.60 (s, 1H), 7.11–7.18 (m, 3H), 4.25 (m, 1H), 4.05 (q, 2H), 3.75 (m, 1H), 3.35 (m, 3H), 2.80 (m, 2H), 2.45 (m, 2H), 1.75 (m, 1H), 1.7 (t, 3H), 1.05 (m, 2H); MS(Cl) *m/z* 461 (MH⁺); Anal. (C₂₂H₂₂BrClN₃O₂) C, H, N.

Dealkylation of 10a and 10b by the above procedure afforded 11a and 11b.

(*E*)-Ethyl-3-(3-bromo-8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-piperidinecarboxylate (11b). (foam 47%); ¹H NMR (300 MHz, CDCl₃) δ 8.45 (d, 1H), 7.60 (d, 1H), 7.11–7.16 (m, 4H), 4.25 (m, 1H), 4.0 (q, 2H), 3.75 (m, 1H), 3.35 (m, 3H), 2.80 (m,

2H), 2.45 (m, 2H), 1.75 (m, 1H), 1.7 (t, 3H), 1.0 (m, 2H); MS(Cl), *m/z* 383 (MH⁺).

(*E*)-Ethyl-3-(3-bromo-8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-pyrrolidene-carboxylate (11a). (49%); ¹H NMR (300 MHz, CDCl₃) δ 8.4 (d, 1H, *J* = 4.7 Hz), 7.4 (d, 1H, *J* = 6.8 Hz), 7.1–7.3 (m, 4H), 4.2–4.3 (m, 1H), 4.05–4.15 (q, 2H, *J* = 7.2 Hz), 3.6–3.8 (m, 2H), 3.2–3.4 (m, 3H), 3.0–3.2 (m, 1H), 2.7–3.0 (m, 2H), 2.4–2.5 (m, 1H), 1.2 (t, 3H, *J* = 7.2 Hz); ¹³C (75 MHz, CDCl₃) δ 156.08, 155.24, 146.77, 139.85, 138.09, 133.48, 133.17, 130.00, 128.73, 126.71, 122.55, 61.25, 50.38, 49.84, 45.86, 45.66, 32.20, 31.76, 31.16, 30.51, 15.03; MS(Cl), *m/z* 369 (MH⁺); Anal. (C₂₁H₂₁N₂O₂Cl) C, H, N.

(*E*)-3-Bromo-8-chloro-6,11-dihydro-11-(3-piperidinylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (12c). A solution of 11c (170 mg, 0.36 mmol) in concn HCl (2 mL) was stirred at 80°C overnight, then cooled to 0°C, diluted with H₂O (10 mL), basified with 10% NaOH (10 mL) and extracted with CH₂Cl₂ (3 × 50 mL). The organic layer was separated, washed with H₂O (20 mL), and the solvent was evaporated yielding a solid, which was recrystallized from CH₂Cl₂:Et₂O as white crystals (140 mg, 97%); mp 166–167°C; ¹H NMR (300 MHz, CDCl₃) δ 8.46 (s, 1H), 7.60 (s, 1H), 7.15 (s, 1H), 7.11 (d, 1H), 7.05 (d, 1H), 3.55 (d, 1H), 3.39 (d, 1H), 3.0 (m, 1H), 2.85 (m, 3H), 2.40 (m, 2H), 2.0 (m, 2H), 1.75 (m, 1H), 1.55 (m, 1H); MS(Cl) *m/z* 389 (MH⁺); Anal. (C₁₉H₁₈BrClN₃·0.25H₂O) C, H, N.

This procedure was used to convert 11a and 11b to 12a, 12b.

(*E*)-8-Chloro-6,11-dihydro-11-(3-piperidinylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (12b). (90%); mp 139–140°C; ¹H NMR (300 MHz, CDCl₃) δ 8.40 (d, 1H), 7.45 (d, 1H), 7.10 (m, 4H), 3.55 (d, 1H), 3.39 (m, 3H), 3.0 (m, 1H), 2.85 (m, 3H), 2.41 (m, 2H), 1.75 (m, 1H), 1.55 (m, 1H); MS(Cl) *m/z* 311 (MH⁺); Anal. (C₁₉H₁₈ClN₃) C, H, N.

(*E*)-8-Chloro-6,11-dihydro-11-(3-pyrrolylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (12a). (76%); ¹H NMR (300 MHz, CDCl₃) δ 8.4 (d, 1H, *J* = 4.7 Hz), 7.4 (d, 1H, *J* = 7.7 Hz), 7.02–7.24 (m, 4H), 3.2–3.4 (m, 3H), 3.0–3.2 (m, 3H), 2.7–2.9 (m, 3H); MS (Cl) *m/z* 297 (MH⁺) HRMS calcd. (MH⁺) for (C₁₈H₁₆N₃Cl) 297.1159, measured 297.1153.

(*Z*)-3-(8-Chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-*N*-phenyl-1-piperidinecarboxamide (21). Triethylamine (0.2 mL, 2.72 mmol) was added to a solution of the amine (9b) (70 mg, 0.225 mmol) and phenylisocyanate (0.2 mL, 1.53 mmol) in CH₂Cl₂ (15 mL) at 0°C. The reaction was stirred overnight at

20°C. The reaction was quenched by addition of H₂O (15 mL), and the organic layer was separated, dried and chromatographed on silica gel eluting with 20% v/v EtOAc:Hexanes as a white foam, which crystallized from Ether (10 mL) as white crystals (75 mg, 78%); mp 184–185°C; ¹H NMR (300 MHz, CDCl₃) δ 10.05 (brs, 1H), 8.20 (d, 1H), 7.30 (dd, 2H), 7.0–7.4 (m, 8H), 4.75 (d, 1H), 4.50 (m, 1H), 3.50 (m, 1H), 3.30 (m, 2H), 2.90 (m, 2H), 2.80 (m, 1H), 2.60 (m, 1H), 2.05 (m, 1H), 1.75 (m, 2H); MS(Cl) *m/z* 430 (MH⁺); Anal. (C₂₆H₂₄ClN₃O) C, H, N.

(Z)-3-(8-Chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-piperidinocarbothioic acid *S*-phenyl ester (22). Phenylchlorothioformate (0.2 g, 1.13 mmol) was added to a solution of 9b (25 mg, 0.0806 mmol) and triethylamine (0.2 mL, 2.72 mmol) in pyridine (2 mL) at 0°C. 4-Dimethylamino pyridine, DMAP (5 mg, 0.0416 mmol) was added and the solution stirred at 20°C overnight. The solvent was evaporated, and the residue extracted with EtOAc (25 mL), washed with H₂O (20 mL) and chromatographed on silica gel eluting with 5% v/v MeOH/EtOAc as a solid, which was triturated with hexanes yielding a white solid (30 mg, 83%); mp 187–188°C; ¹H NMR (300 MHz, CDCl₃) δ 8.42 (d, 1H), 7.48 (d, 1H), 7.37 (m, 2H), 7.16 (s, 1H), 7.14 (d, 1H), 4.52 (d, 1H), 3.95 (d, 1H), 3.45 (m, 3H), 3.10 (m, 1H), 2.85 (m, 2H), 2.55 (m, 2H), 1.85 (m, 1H), 1.65 (m, 1H); MS (Cl) *m/z* 447 (MH⁺); HRMS calcd (MH⁺) for C₂₆H₂₄ClN₂OS 447.1298, measured 447.1297; Anal. (C₂₆H₂₃ClN₂OS·2H₂O) C, H, N.

(Z)-3-(8-Chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-((4-pyridinyl)acetyl)-piperidine (17). 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide, EDCI (50 mg, 0.26 mmol) and 1-hydroxybenzotriazole, HOBT (40 mg, 0.296 mmol) were added sequentially to a solution of 9b (50 mg, 0.161 mmol) and 4-pyridylacetic acid (30 mg, 0.22 mmol) in DMF (5 mL) and *N*-methylmorpholine, NMM (0.5 mL) at 0°C, then stirred overnight at 20°C. The solvent was evaporated under reduced pressure, and the residual oil extracted with EtOAc (50 mL), washed with H₂O (25 mL), dried and chromatographed on silica gel eluting with 5% v/v MeOH:EtOAc containing 2% v/v NH₄OH, yielding the product as a white solid (foam, 52 mg, 75%); ¹H NMR (300 MHz, CDCl₃) δ 8.55 (d, 1H), 8.43 (dd, 2H), 7.48 (d, 1H), 7.09–7.20 (m, 4H), 6.83 (dd, 1H), 4.35 (d, 1H), 4.20 (m, 1H), 4.05 (d, 1H), 3.65 (m, 1H), 3.45 (d, 1H), 3.35 (d, 1H), 3.25 (m, 2H), 2.80 (m, 2H), 2.40 (m, 2H), 1.77 (m, 1H), 1.55 (m, 1H); MS(Cl) *m/z* 430 (MH⁺); Anal. (C₂₆H₂₄N₃ClO·H₂O) C, H, N.

(E)-3-(8-Chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-((4-pyridinyl)acetyl)-piperidine (48). The procedure as described for 17 was used to acylate 12b, to obtain 48 as a white solid (foam, 73%);

¹H NMR (300 MHz, CDCl₃) δ 8.55 (d, 1H), 8.43 (dd, 2H), 7.48 (d, 1H), 7.09–7.23 (m, 4H), 7.06 (d, 1H), 6.72 (d, 1H), 4.50 (m, 1H), 4.35 (d, 1H), 3.65 (d, 1H), 3.60 (d, 1H), 3.35 (d, 1H), 3.25 (m, 2H), 3.15 (d, 1H), 2.85 (m, 2H), 2.45–2.60 (m, 2H), 1.75 (m, 1H), 1.65 (m, 1H); MS(Cl) *m/z* 430 (MH⁺); Anal. (C₂₆H₂₄N₃ClO·1.25 H₂O) C, H, N.

Compounds 15–20, 45–50, 63–65. The acylation procedure described for 17 was used to prepare these *N*-acyl compounds.

Compound 41: ¹H NMR (300 MHz, CDCl₃) δ 8.39 (d, 1H, *J* = ~3 Hz), 7.81 (apparent d, 2H, *J* = 7.4 Hz), 7.50–7.64 (m, 3H), 7.41 (d, 1H, *J* = 6.7 Hz), 7.08–7.20 (m, 4H), 4.27 (d, 2H, *J* = 15.4 Hz), 3.84 (d, 1H, *J* = 15.4 Hz), 3.10–3.40 (m, 4H), 2.60–2.94 (m, 3H), 2.25–2.38 (m, 1H); HRMS calcd (MH⁺) for (C₂₄H₂₁N₃O₂ClS) 437.1087, measured 437.1091.

Compound 42: ¹H NMR (300 MHz, CDCl₃) δ 8.39 (d, 1H, *J* = 4.7 Hz), 7.81 (apparent d, 2H, *J* ~7 Hz), 7.50–7.64 (m, 3H), 7.41 (d, 1H, *J* = 7.6 Hz), 7.08–7.21 (m, 5H), 4.28 (d, 1H, *J* = 15.2 Hz), 3.86 (dd, 1H, *J* = 1.6, 15.2 Hz), 3.2–3.4 (m, 4H), 2.60–2.95 (m, 3H), 2.25–2.40 (m, 1H); HRMS calcd (MH⁺) for (C₂₄H₂₂N₂O₂S) 403.1480, measured 403.1480.

Compound 43: ¹H NMR (300 MHz, CDCl₃) δ 8.4 (d, 1H, *J* = 4.7), 7.56–7.64 (m, 2H), 7.42 (d, 1H, *J* = 7.3 Hz), 7.10–7.20 (m, 5H), 4.34 (d, 1H, *J* = 15.6 Hz), 3.85 (d, 1H, *J* = 15.5 Hz), 3.36 (apparent t, 2H, *J* = 7.1 and 7.4 Hz), 3.16–3.26 (m, 2H), 2.80–2.94 (m, 1H), 2.64–2.78 (m, 2H), 2.30–2.42 (m, 1H); HRMS calcd. (MH⁺) for (C₂₃H₁₉N₂O₂ClS₂) 443.0655, measured 443.0649.

Compound 44: ¹H NMR (300 MHz, CDCl₃) δ 8.40 (d, 1H, *J* = ~3 Hz), 7.56–7.62 (m, 2H), 7.4 (d, 1H, *J* = 7.0 Hz), 7.01–7.21 (m, 6H), 4.36 (d, 1H, *J* = 15.4 Hz), 3.85 (d, 1H, *J* = 15.4 Hz), 3.36 (apparent t, 2H, *J* = 6.8 and 7.7 Hz), 3.15–3.30 (m, 2H), 2.80–2.94 (m, 1H), 2.60–2.80 (m, 2H), 2.30–2.42 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 155.16, 146.40, 139.32, 138.26, 138.14, 137.94, 135.83, 135.08, 133.20, 132.42, 131.85, 128.45, 128.22, 127.81, 127.52, 126.17, 122.34, 52.05, 47.51, 32.38, 31.37, 30.67. HRMS calcd. (MH⁺) for (C₂₂H₂₀N₂OS) 448.1259, measured 448.1250.

Compound 45: ¹H NMR (300 MHz, CDCl₃) δ 8.36–8.44 (m, 3H), 7.43 (dd, 1H, *J* = 1.6, 7.8 Hz), 7.05–7.35 (m, 6H), 4.91 (d, 1H, rotomer A, *J* = 15.9 Hz), 4.67 (d, 1H, rotomer B, *J* = 17.9 Hz), 3.88–4.08 (m, 1H), 3.48–3.82 (m, 5H), 3.2–3.4 (m, 2H), 2.72–3.02 (m, 2H), 2.40–2.62 (m, 1H); HRMS calcd (MH⁺) for (C₂₃H₂₂N₃OClS) 448.1250, measured 448.1248.

Compound 46: ^1H NMR (300 MHz, CDCl_3) δ 8.48–8.58 (m, 2H), 8.39–8.46 (m, 1H), 7.44 (dd, 1H, $J = 1.2$, 7.5 Hz), 7.08–7.26 (m, 6H), 4.81 (d, 1H, rotomer A, $J = 15.9$ Hz), 4.66 (d, 1H, rotomer B, $J = 17.9$ Hz), 4.0 (d, 1H, $J = 17.1$ Hz), 3.9 (d, 1H, $J = 15$ Hz), 3.54–3.76 (m, 2H), 3.18–3.44 (m, 3H), 2.7–3.0 (m, 3H), 2.38–2.58 (m, 1H); Anal. ($\text{C}_{25}\text{H}_{22}\text{N}_3\text{OCl}$) C, H, N.

Compound 61: ^1H NMR (300 MHz, CDCl_3) δ 7.74–7.80 (m, 2H), 7.40–7.66 (m, 4H), 7.04–7.22 (m, 4H), 3.9 (d, 1H, $J = 14.6$ Hz), 3.7 (d, 1H, $J = 14.8$ Hz), 3.3–3.4 (m, 2H), 3.04–3.24 (m, 3H), 2.66–2.90 (m, 2H), 2.30–2.41 (m, 1H); HRMS calcd (MH^+) for ($\text{C}_{25}\text{H}_{21}\text{N}_3\text{O}_2\text{ClS}$) 437.1092, measured 437.1091.

Compound 63: ^1H NMR (300 MHz, CDCl_3) δ 8.30–8.42 (m, 3H), 7.30–7.50 (m, 1H), 7.02–7.25 (m, 6H), 4.89 (d, 1H, rotomer A, $J = 16$ Hz), 4.66 (d, 1H, rotomer B, $J = 18$ Hz), 3.6–4.04 (m, 4H), 3.10–3.36 (m, 3H), 2.70–3.00 (m, 3H), 2.40–2.56 (m, 1H); HRMS calcd (MH^+) for ($\text{C}_{25}\text{H}_{22}\text{N}_3\text{OClS}$) 448.1255, measured 448.1250.

Compound 62: ^1H NMR (300 MHz, CDCl_3) δ 8.4 (bs, 1H), 7.45–7.65 (m, 3H), 7.10–7.30 (m, 5H), 3.99 (d, 1H, $J = 15.1$ Hz), 3.75 (d, 1H, $J = 15$ Hz), 3.38–3.46 (m, 2H), 3.15–3.30 (m, 3H), 2.70–2.90 (m, 2H), 2.33–2.44 (m, 1H); HRMS calcd (MH^+) for ($\text{C}_{25}\text{H}_{21}\text{N}_3\text{O}_2\text{ClS}_2$) 443.0654, measured 443.0655.

Compound 64: ^1H NMR (300 MHz, CDCl_3) δ 8.5 (bs, 2H), 4.4 (d, 1H, $J = 4.6$ Hz), 7.4 (d, 1H, $J = 7.3$ Hz), 7.10–7.26 (m, 7H), 7.30–7.44 (m, 1H), 3.70–3.88 (m, 2H), 3.06–3.58 (m, 6H), 2.70–3.00 (m, 2H), 2.44–2.62 (m, 1H); HRMS calcd (MH^+) for ($\text{C}_{25}\text{H}_{22}\text{N}_3\text{OCl}$) 416.1550, measured 416.1530.

Compound 65: ^1H NMR (300 MHz, CDCl_3) δ 8.4 (d, 1H, $J = 3.0$ Hz), 7.12–7.60 (m, 7H), 6.7 (bs, 1H), 4.85–4.52 (m, 1H), 3.80–4.20 (m, 2H), 3.20–3.70 (m, 4H), 2.70–3.00 (m, 2H), 2.45–2.65 (m, 1H); HRMS calcd (MH^+) for ($\text{C}_{25}\text{H}_{19}\text{N}_2\text{O}_2\text{Cl}$) 391.1218, measured 391.1213.

(*E*)-8-Chloro-6,11-dihydro-11-[(4-nitrophenylthio)-3-piperidinylidene]-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (51). 4-Nitrobenzenesulfonyl chloride (130 mg, 0.65 mmol) was added to a solution of 12b (100 mg, 0.322 mmol) in methylene chloride (3 mL) at 20 °C. Triethylamine (0.3 mL) was added and the solution stirred overnight. Water (20 mL) was added and the reaction was extracted with methylene chloride (25 mL). The organic layer was separated, dried and chromatographed on silica gel eluting with 20% v/v EtOAc:hexanes yielding an oil, which crystallized from methanol as yellow crystals (100 mg, 66%); mp 173–174 °C; MS(Cl^-) m/z 464 (MH^+); ^1H NMR (300 MHz, CDCl_3) δ 8.47 (d,

1H), 8.10 (d, 2H), 7.65 (d, 1H), 7.28–7.31 (m, 4H), 7.07 (s, 2H), 3.77 (q, 2H), 3.55 (m, 2H), 3.25 (m, 1H), 3.15 (m, 1H), 2.91 (m, 2H), 2.45 (m, 2H), 1.82 (m, 2H); Anal. ($\text{C}_{25}\text{H}_{22}\text{ClN}_3\text{O}_2\text{S}$) C, H, N.

(*E*)-3-(3-Bromo-8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-[(5-chloro-2-thienyl)sulfonyl]-piperidine (60). Method A. 5-Chloro thiophene-2-sulfonyl chloride (0.2 g, 0.921 mmol) was added to a solution of 12c (80 mg, 0.204 mmol) in pyridine (2 mL) at 0 °C. DMAP (3 mg, 0.0245 mmol) was added, and the solution was stirred at 20 °C overnight. The solvent was evaporated under reduced pressure, and the residue extracted with methylene chloride (40 mL), and the crude product was chromatographed on silica gel eluting with 20% EtOAc:hexanes as a solid which recrystallized from ether (15 mL) as white crystals (70 mg, 59.8%); mp 171–172 °C; ^1H NMR (300 MHz, CDCl_3) δ 8.45 (s, 1H), 7.60 (s, 1H), 7.20 (s, 1H), 7.16 (m, 2H), 7.08 (d, 1H), 6.91 (d, 1H), 3.79 (d, 1H), 3.63 (d, 1H), 3.2–3.5 (m, 3H), 3.05 (m, 1H), 2.85 (m, 2H), 2.35 (m, 2H), 1.85 (m, 1H), 1.65 (m, 1H); MS (Cl^-) m/z (569 (MH^+)); Anal. ($\text{C}_{25}\text{H}_{19}\text{BrCl}_2\text{N}_3\text{O}_2\text{S}_2$) C, H, N, S.

(*Z*)-3-(3-Bromo-8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-[(5-chloro-2-thienyl)sulfonyl]-piperidine (38). Prepared from 9c by following Method A described for 60. Obtained 38 as white crystals (65.4%); mp 165–167 °C; ^1H NMR (300 MHz, CDCl_3) δ 8.47 (s, 1H), 7.64 (s, 1H), 7.20 (s, 1H), 7.16 (m, 2H), 7.08 (d, 1H), 6.93 (d, 1H), 4.25 (d, 1H), 3.75 (d, 1H), 3.51 (d, 1H), 3.37 (m, 2H), 2.79 (m, 3H), 2.48 (m, 1H), 2.10 (m, 1H), 1.85 (m, 1H), 1.65 (m, 1H); MS(Cl^-) m/z 569 (MH^+); Anal. ($\text{C}_{25}\text{H}_{19}\text{BrCl}_2\text{N}_3\text{O}_2\text{S}_2$) C, H, N. The above Method A was used to prepare sulfonamides 23–35, 37–44, 52–58, and 60–62.

(*Z*)-3-(8-Chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-(3-pyridinesulfonyl)-piperidine (36) and (*Z*)-3-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-[(4-nitrophenyl)sulfonyl]-piperidine (27). Method B. 4-Nitrobenzenesulfonyl chloride (100 mg, 0.406 mmol) was added to a solution of 3-pyridinesulfonyl acid (100 mg, 0.626 mmol) in pyridine (3 mL) at 0 °C. DMAP (5 mg) was added and the mixture stirred at 0 °C for 7 h. (*Z*)-8-Chloro-6,11-dihydro-11-(3-[(piperidinylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (9b) (80 mg) was added and the mixture stirred 1 h at 0 °C, then overnight at 20 °C. Water (25 mL) and CH_2Cl_2 (50 mL) were added and the organic layer separated, washed with water (10 mL), dried, and chromatographed on silica gel eluting with 20% v/v EtOAc:Hexanes to afford the less polar product 27, which was recrystallized from methanol as white crystals (37 mg, 15%); mp 178–179 °C; MS(Cl^-) m/z 496 (MH^+); ^1H NMR (300 MHz, CDCl_3) δ 8.43 (d,

1H). 8.32 (d, 2H), 7.88 (d, 2H), 7.48 (d, 1H), 7.15–7.19 (m, 3H), 7.02 (d, 1H), 4.31 (d, 1H), 3.75 (d, 1H), 3.50 (d, 1H), 3.34 (m, 2H), 2.78 (m, 3H), 2.50 (m, 1H), 2.10 (m, 1H), 1.75 (m, 1H), 1.65 (m, 1H); Anal. (C₂₅H₂₂ClN₃O₄S) C, H, N. Compound 36 was eluted with 5% v/v MeOH:EtOAc containing 1% NH₄OH yielding a solid that was crystallized from ether as white crystals (180 mg, 68.9%); mp 158–159°C; ¹H NMR (300 MHz, CDCl₃) δ 8.87 (s, 1H), 8.80 (d, 1H), 8.48 (d, 1H), 7.95 (d, 1H), 7.5 (m, 2H), 7.19 (m, 3H), 7.04 (d, 1H), 4.38 (d, 1H), 3.80 (d, 1H), 3.45 (m, 3H), 2.85 (m, 3H), 2.50 (m, 1H), 2.05 (m, 1H), 1.75 (m, 1H), 1.65 (m, 1H); MS(Cl) *m/z* 452 (MH⁺) Anal. (C₂₄H₂₂ClN₃O₂S) C, H, N.

(*E*)-3-(8-Chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-(3-pyridinesulfonyl)-piperidine (59) and (*E*)-3-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-[(4-nitrophenyl)sulfonyl]-piperidine (55). Prepared from 12b by using Method B described for 36. The less polar sulfonamide 55 was obtained as white crystals from methanol (25%); mp 232–233°C; ¹H NMR δ 8.39 (d, 1H), 8.31 (d, 2H), 7.88 (d, 2H), 7.43 (d, 1H), 7.09–7.15 (m, 3H), 7.06 (d, 1H), 3.84 (d, 1H), 3.58 (d, 1H), 3.55 (m, 1H), 3.25 (m, 2H), 3.10 (m, 1H), 2.80 (m, 2H), 2.35 (m, 2H), 1.85 (m, 1H), 1.65 (m, 1H); MS(Cl) *m/z* 496 (MH⁺); Anal. (C₂₅H₂₂ClN₃O₄S) C, H, N. The major product 59 was obtained as white crystals (67%); mp 214–215°C; ¹H NMR (300 MHz, CDCl₃) δ 8.89 (s, 1H), 8.80 (d, 1H), 8.48 (d, 1H), 7.95 (d, 1H), 7.45 (m, 2H), 7.15 (m, 3H), 7.08 (d, 1H), 3.85 (d, 1H), 3.55 (d, 1H), 3.50 (m, 1H), 3.65 (m, 2H), 3.05 (m, 1H), 2.75 (m, 2H), 2.33 (m, 2H), 1.85 (m, 1H), 1.75 (m, 1H); MS(Cl) *m/z* 452 (MH⁺); Anal. (C₂₄H₂₂ClN₃O₂S) C, H, N.

Acknowledgements

The authors thank Dr M. Puar and staff for the NMR studies, the Analytical services group for physical data, and Drs A. K. Ganguly and S. McCombie for helpful chemical discussions.

References and Notes

- For leading references describing the biology of *ras* see: (a) Barbucid, M. *Ann. Rev. Biochem.* 1987; (b) Bos, J. L. *Cancer Res.* 1989, 49, 4682.
- (a) Egan, S. E.; Weinberg, R. A. *Nature* (London) 1993, 365, 781; (b) Marshall, M. S. *Trends Biochem. Sci.* 1993, 18, 250; (c) Hall, A. *Science* 1994, 264, 1413.
- Boguski, M. S.; McCormick, F. *Nature* (London) 1993, 366, 643.
- (a) Nishida, E.; Gotoh, Y. *Trends Biochem. Sci.* 1993, 18, 128; (b) Stokoe, D.; MacDonald, S. G.; Caldwell, K.; Symons, M.; Hancock, J. F. *Science* 1994, 264, 1463; (c) Leever, S. J.; Paterson, H. F.; Marshall, C. J. *Nature* (London) 1994, 369, 411.
- (a) Casey, P. J.; Soliski, P. A.; Der, C. J.; Buss, J. E. *Proc. Nat. Acad. Sci. U. S. A.* 1989, 86, 8323; (b) Zhang, F. L.; Casey, P. J. *Ann. Rev. Biochem.* 1996, 65, 241.
- (a) Casey, P. J.; Thissen, J. A.; Moomaw, J. F. *Proc. Natl. Acad. Sci. U.S.A.* 1991, 88, 8631; (b) Yokoyama, K.; Goodwin, G.; Ghomashchi, F.; Glomset, J. A.; Gelb, M. H. *ibid.* 1991, 88, 5302.
- (a) Gibbs, J. B.; Oliff, A.; Kohl, N. E. *Cell* 1990, 62, 81; (b) Gibbs, J. B. *Cell* 1991, 65, 1; (c) Gibbs, J. B.; Oliff, A.; Kohl, N. E. *Cell* 1994, 77, 175; (d) Kohl, N. E.; Conner, M. W.; Gibbs, J. B.; Graham, S. L.; Hurtman, G. D.; Oliff, A. J. *Cell. Biochem.* 1995, Suppl. 22, 145.
- We have previously reported *Ras* inhibition based on blocking the nucleotide-exchange process: (a) Wolin, R.; Wang, D.; Kelly, J.; Afonso, A.; James, L.; Kirschmeier, P.; McPhail, A. *Bioorg. Med. Chem. Lett.* 1996, 6, 195. And by a novel mechanism: (b) Kumar, C. C.; Prorock-Rogers, C.; Kelly, J.; Dong, Z.; Lin, J.; Armstrong, L.; Kung, H.; Weber, M. J.; Afonso, A. *Cancer Res.* 1999, 59, 5106.
- James, G. L.; Goldstein, J. L.; Brown, M. S. *J. Biol. Chem.* 1995, 270, 6221.
- Zhang, F. L.; Kirschmeier, P.; Carr, D.; James, L.; Bond, R. W.; Wang, L.; Patton, R.; Windsor, W. T.; Syto, R.; Zhang, R.; Bishop, R. W. *J. Biol. Chem.* 1997, 272, 10232.
- Whyte, D. B.; Kirschmeier, P.; Hockenberry, T. N.; Nunez-Olivia, I.; James, L.; Catino, J. L.; Bishop, R. W.; Pal, J.-K. *J. Biol. Chem.* 1997, 272, 14459.
- (a) Leftheris, K.; Kline, T.; Vite, G. D.; Cho, Y. H.; Bhide, R. S.; Patel, D. V.; Patel, M. M.; Schmidt, R. J.; Weller, H. N.; Andahazy, M. L.; Carboni, J. M.; Gullo-Brown, J. L.; Lee, F. Y. F.; Ricca, C.; Rose, W. C.; Yan, N.; Barbacid, M.; Hunt, J. T.; Meyers, C. A.; Seizinger, B. R.; Zahler, R.; Manne, V. J. *J. Med. Chem.* 1996, 39, 224. For recent reviews covering most of the reported FPT inhibitors, see: (b) Kaloustian, S. A.; Skotnicki, J. S. *Ann. Reports Med. Chem.* 1996, 31, 171; (c) Graham, S. L. *Exp. Opin. Ther. Patents* 1995, 5, 1269; (d) Qian, Y.; Vogt, A.; Sebti, S. M.; Hamilton, A. D. *J. Med. Chem.* 1996, 39, 217.
- (a) Hunt, J. H.; Lee, V. G.; Leftheris, K.; Seizinger, B.; Carboni, J.; Mabius, J.; Ricca, C.; Yan, N.; Manne, V. J. *Med. Chem.* 1996, 39, 353; (b) Leonard, D. M.; Shuler, K. R.; Poulter, C. J.; Eaton, S. R.; Sawyer, T. K.; Hodges, J. C.; Su, T. Z.; Scholten, J. D.; Gowan, R. C.; Sebati-Leopold, J. S.; Doherty, A. M. *J. Med. Chem.* 1997, 40, 192.
- (a) Bishop, R. W.; Bond, R.; Petrin, J.; Wang, L.; Patton, R.; Doll, R.; Njoroge, G.; Catino, J.; Schwartz, J.; Windsor, W.; Syto, R.; Schwartz, J.; Carr, D.; James, L.; Kirschmeier, P. *J. Biol. Chem.* 1995, 270, 30611; (b) I has an FPT IC₅₀ of 0.25 μM.
- For more recent reports on structures related to I see: (a) Mallams, A. K.; Njoroge, G.; Doll, R. J.; Snow, M. E.; Kaminski, J. J.; Rossman, R.; Vibulphun, B.; Bishop, W. R.; Kirschmeier, P.; Liu, M.; Bryant, Petrin, J.; Remiszewski, S.; Taveras, A.; Wang, S.; Wong, J.; Catino, J.; Girijavallabhan, V.; Ganguly, A. K. *Bioorg. Med. Chem. Lett.* 1997, 5, 93; (b) Njoroge, G.; Doll, R. J.; Vibulphun, B.; Alvarez, C.; Bishop, W. R.; Petrin, J.; Kirschmeier, P.; Curruthers, N. I.; Wong, J.

Albanese, M.; Piwinski, J. J.; Catino, J.; Girijavallabhan, V.; Ganguly, A. K. *Bioorg. Med. Chem.* 1997, 5, 101; (c) Njoroge, G.; Vibulbhan, B.; Alvarez, C.; Bishop, W. R.; Petrin, J.; Doll, R. J.; Girijavallabhan, V.; Ganguly, A. K. *Bioorg. Med. Chem. Lett.* 1996, 6, 2977.

16. The terms 4-piperidino, 3-piperidino and 3-pyrrolidino are used for convenience to denote the carbon of the pendant piperidine or pyrrolidine ring that forms the olefinic bond at C-11 of the benzocycloheptapyridine tricycle.

17. Villani, F. J.; Daniels, P. J. L.; Ellis, C. A.; Mann, T. A.; Wang, K. C. *J. Heterocycl. Chem.* 1971, 8, 73.

18. Wong, J. K.; Piwinski, J. J.; Green, M. J.; Ganguly, A. K.; Anthas, J. C.; Billah, M. M. *Bioorg. Med. Chem. Lett.* 1993, 3, 1073.

19. (a) The olefinic geometries were established by NMR studies wherein an NOE effect in the Z-isomers 3b was observed

between the C-10 proton and the allylic protons on the lactam ring. (b) X-Ray crystallographic data on 6b and 5b is available from the authors. (c) The mixed sulfonic anhydride 14 obtained by reacting 3-pyridinesulfonic acid with *p*-nitrobenzenesulfonyl chloride (Scheme 2) was used to prepare the 3-pyridyl-sulfonamides 36 and 59.

20. The chemical shifts of the allylamino protons in the sulfonamide derivatives of Z-compounds II are deshielded by 0.2-0.3 ppm relative to the corresponding derivatives of the E-compounds III.

21. FPT and GGPT assays were performed over a wide range of inhibitor concentrations in half-log increments. Each data point was typically generated by duplicate determinations and the mean value was used to calculate percent inhibition relative to a vehicle (DMSO) control. Duplicates were within $\pm 5\%$ of the mean value.